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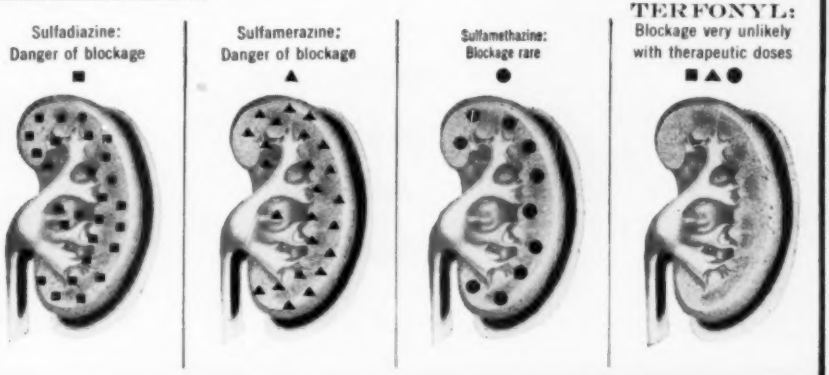

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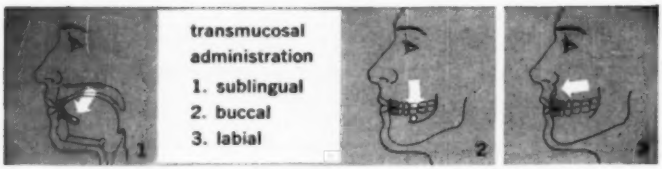

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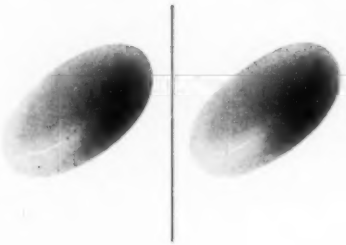

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

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VOL. 26, NO. 6 JUNE 1950

SYMPOSIUM ON INHALATIONAL THERAPY

*ANOXIA IN CLINICAL MEDICINE**

THE ORIGINS AND EFFECTS OF ANOXIA

VIRGIL HOLLAND MOON
Professor of Pathology, Emeritus, Jefferson Medical College, Philadelphia

THE term *anoxia*, as used in this discussion, will denote a reduction of oxygen below physiologic levels in the tissues of the body. Space is lacking to review the literature pertinent to this subject, and only a summary of the origins and effects of anoxia will be attempted.

Anoxic conditions have been grouped according to origins (Blalock[1]). Insufficient delivery of oxygen by the lungs to the blood is called *anoxic anoxia*. It develops in respiratory deficiency and in various forms of pulmonary disease and asphyxia. Insufficient oxygen during anesthesia belongs in this group. *Anemic anoxia* results from a deficiency of red cells or of hemoglobin in the blood, as in anemia or after hemorrhage. The inactivation of hemoglobin by carbon monoxide produces a similar effect. The term *stagnant anoxia* indicates circulatory deficiency as in passive congestion, cardiac failure or shock. The respiration is not primarily affected; the blood has access to oxygen in the lungs, but transportation of it to the tissues is retarded.

* Given December 5, 1949 by The New York Academy of Medicine in cooperation with the New York Association of Oxygen and Ambulance Services, Inc.

The term *histotoxic anoxia* is applied to the poisonous effects of cyanides, alcohol and certain narcotics as chloretone and barbiturates often used in anesthesia. These are said to inhibit the utilization of oxygen by the tissues. The effects are as if the supply of oxygen had been shut off. The cells seem too intoxicated to utilize the oxygen supplied and transported to them in normal amount.

Most instances of anoxia will fall into one or another of these categories, but regardless of how the deficiency developed the effects are similar. The functional capacity of all tissues is lowered in proportion to the degree and the duration of the oxygen lack. Metabolic and enzymatic activities are reduced or inhibited, as is well understood. But more obscure and of the highest importance are the effects upon *fluid balance*, upon the *peripheral circulation* and upon *renal function*.

Fluid Balance.—Attention is invited first to the mechanism by which anoxia disturbs fluid balance and thereby causes far-reaching functional disorders. Fluid balance refers to the delicate mechanisms which regulate the volume of body fluid and govern its movement in either direction between the blood and the tissues. This is largely a function of normal capillary endothelium.

Half a century ago, Starling[2] showed that lymph and tissue fluids are derived from the blood by the permeation of watery fluid and salts through the capillary walls. Normal endothelium permits the passage of water and of crystalline solutes through the walls in either direction, but it is relatively impermeable to the plasma colloids. He showed that various agents, called capillary poisons, may damage endothelium and thereby increase its permeability so that the plasma proteins may leak out into the tissue spaces. This results in an increased flow of lymph which has a high content of plasma colloids. These observations have been confirmed and amplified by eminent physiologists including Ebbecke,[3] Krogh,[4] Lewis,[5] Landis,[6] Drinker,[7] and others. Landis concluded that any type of injury, *including anoxia*, to capillary walls increases their permeability. He showed that the obstruction of an artery for three minutes caused a four-fold increase of endothelial permeability in the area supplied by that artery.

The movement of fluid between the blood and the tissues depends upon several factors including capillary blood pressure and the osmotic attraction of the plasma colloids. But the action of these forces in maintaining a physiologic balance between the intravascular and extra-

vascular fluids depends absolutely upon the presence of a normal semipermeable membrane between them. When the endothelium becomes abnormally permeable, then osmosis ceases to act and the mechanism of fluid balance is thrown out of gear. Endothelium so permeable as to allow the plasma proteins to leak through it, is incapable either of producing or of maintaining physiologic relationships between the intravascular and extravascular fluids. There is an increase in tissue fluid and in lymph flow; ability to absorb fluids is lost, those given by mouth are vomited and those given by rectum or by hypodermoclysis are not absorbed.

These changes affect the mechanisms by which the volume and the concentration of the blood are maintained. Under normal conditions, fluid lost by hemorrhage or otherwise is replaced rapidly by the absorption of fluid from the tissues so that the volume of blood in circulation is restored and maintained. When fluid balance is upset, absorption does not occur but the movement of fluid is in the opposite direction *from* the blood *into* the tissues. This process results in anhydremia or hemoconcentration, i.e., an increase in the number of erythrocytes per unit volume of blood. These disturbances of fluid balance are among the serious but obscure effects of anoxia.

Peripheral Circulatory Effects, Shock.—Studies on capillaries have shown that these are not simple collapsible tubes; their walls have tonus and contractility independent of the adjacent vessels and of innervation. In resting tissues, most capillaries are contracted and bloodless but during functional activity they become relaxed, dilated and filled with blood. Anoxia, if severe, produces atony, that is, inability to contract. Krogh[4] found that atony resulted in irreversible stasis when the capillaries were deprived of oxygen for a few minutes. Landis[6] observed that stasis is the surest sign of capillary permeability; this is a form of stagnant anoxia. The areas affected are engorged with blood, which is out of circulation as effectively as if lost by external hemorrhage. Stasis reduces the return flow of venous blood to the heart and thus decreases the systemic circulation of blood.

Stagnant anoxia abolishes functional activity in the tissues and causes the liberation of abnormal metabolites which further disturb the circulation. Years ago, Mann[8] found that the release of ligatures applied to the large vessels of the limbs of dogs resulted in fatal circulatory failure of the shock type. Similar results on wounded men have been

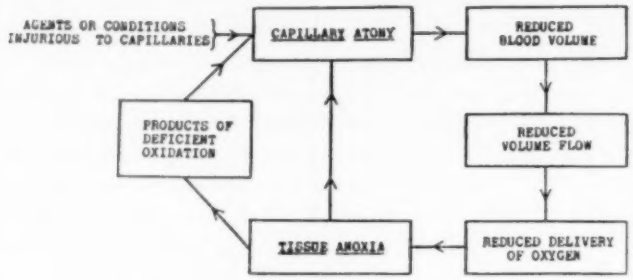

Figure 1.—Reduction of both blood volume and of volume flow results from dilatation and abnormal permeability of capillaries. A reduced delivery of oxygen causes anoxia in the tissues. Lack of oxygen of itself causes dilatation and permeability of capillaries. This relationship gives the mechanism the character of a vicious circle.

reported repeatedly by military surgeons. The release of a tourniquet applied for several hours to a leg has become one of the standard methods for inducing shock experimentally. These facts suggest the formation of abnormal metabolites in anoxic areas, which metabolites cause peripheral circulatory failure when absorbed.

This interpretation was confirmed recently by a new technique. Shorr[9] and his associates externalized mesenteric areas in animals and studied the vascular reactions to various substances. The injection of watery extracts of tissues injured by anoxia or by trauma produced vasodepressor effects. The minute vessels became dilated, engorged, and did not respond to epinephrin nor to other vasoexcitor substances. A similar vasodepressor effect followed the injection of plasma from animals in profound shock. These studies indicated that vasodepressor substances are released from traumatized muscle and from anoxic tissues. The authors believed that the development of shock is due to vascular atony resulting from a preponderance of vasodepressor effects, and that anoxia is a factor causing the circulatory deficiency to progress in a "morbid cycle" to an irreversible stage.

Some fifteen years ago my associates and I came to the same conclusion from evidence of another kind which lacked the delicate precision of the methods used by Shorr. The mechanism of the circulatory failure in shock was pictured in a simple diagram showing the action of factors which cause secondary shock to progress in a vicious circle

toward irreversibility. Let it be emphasized that the two major factors, *Capillary Atony* and *Anoxia*, are reciprocal in their action; either of them originating primarily will presently bring the other into action.

Below are listed the various condition which, in our experience, have terminated in the clinical syndrome of shock with its characteristic changes shown at necropsy, and the agents which we have used successfully in producing shock experimentally.

CLINICAL	EXPERIMENTAL
Trauma, Surgery, Burns	Trauma, Burns
Fulminating infections	Bacterial toxins
Abdominal catastrophes	
Perforations, Peritonitis	Intestinal obstructions
Strangulation, Obstruction	Strangulation
Thrombosis, Pancreatitis	Bile peritonitis
Drugs	Tissue autolysis *in vivo*
Arsenicals	Muscle, liver, brain, kidney
Barbiturates	Barbiturates
Anesthetics	
Sulphonamides	
Poisons	Poisons
$HgCl_2$, As, P, I	$HgCl_2$, As, I
Salicylates	
Serum disease	Anaphylaxis
Transfusion reactions	
Coronary occlusion	
Intoxications	Injections
Icterus gravis	Bile, Cholic salts
Diabetic acidosis	Peptone, Histamine
Pregnancy	
Snake bites	Venoms
Radiation sickness	Radiation (X-ray)
Asphyxia	Asphyxia
High altitude flight	Tourniquet
Heat stroke	Freezing
Hyperthermia (therapeutic)	

For many years the origin of traumatic and surgical shock was uncertain and the literature was confused by controversial discussions. Hence it is gratifying to note that divergent views in large measure have been reconciled. Gradually both clinicians and surgeons have recognized that the occurrence of shock is not limited to trauma, burns and the aftermath of extensive surgery. The same syndrome, with identical physiologic and pathologic features, may develop insidiously in various grave conditions of disease. Harkins[10] listed some thirty conditions in which this may occur. These included freezing, sunburn and

radiation burns, heat stroke; anoxia from any form of asphyxia; thrombosis, intestinal strangulation, bile peritonitis, perforated gastric ulcer, pancreatitis; various poisons such as mercuric chloride, arsenicals, phosphorus, phenols, snake venom; anaphylaxis, transfusion reactions, systemic diseases as eclampsia, toxic jaundice; severe infections as cholera, diphtheria, pneumonia, septicemia, peritonitis, gas gangrene; and last but not least, anesthetic agents including the barbiturates. In any of these conditions the insidious development of anoxia, often terminating in shock, may be expected.

I[11] have verified the occurrence of shock in these conditions and in others not listed by Harkins. Examinations after death from these various causes revealed a characteristic pattern of changes indicative of endothelial damage. These consisted of dilatation and engorgement of minute vessels in the thoracic, abdominal and cranial viscera; petechiae in mucosae, serosae and in solid tissues; edema of visceral tissues, effusions in serous cavities, and acute degeneration ranging to necrosis in the kidneys, brain, liver and myocardium. Our studies indicated that these changes are caused largely by anoxic injury to endothelium and to parenchymatous tissues.

This type of circulatory deficiency occurs in varying degrees and develops with varying rapidity. When severe or profound, it tends to progress inexorably to death; when it is slight or mild, recovery usually follows. When shock is of intermediate or sublethal degree, the patient may live for several days without obvious signs of circulatory failure. Such cases commonly develop one or the other of two serious complications.

Complications.—The first of these is secondary or terminal pneumonia.[12] The visceral hyperemia, stasis and edema affect particularly the lungs. Impaired circulation and abundant albuminous fluid provide ideal conditions for the growth of whatever bacteria may be present in the respiratory tract. The development of secondary pneumonia is almost inevitable unless either death or recovery occurs soon.

The second and most serious complication of sublethal shock is progressive renal insufficiency. In severe shock from whatsoever cause, oliguria or anuria develops immediately; unless circulatory efficiency is restored, this persists and leads to azotemia due to impairment of renal function. I regard this as the most constant, the most serious and the most confusing accompaniment of shock.

This form of renal disease is not new; it was described as "acute Bright's disease" by Osler in the first edition (1892) of *Principles and Practice of Medicine*. He explained it as the action of toxic agents upon the kidneys and noted its occurrence from various poisons, from severe infections such as septicemia, scarlatina, measles, diphtheria, malaria and others, from intoxications as of pregnancy, and from burns. Later Osler added trauma and extensive surgery to the etiologic conditions.

Osler stated that the urine is suppressed or greatly reduced in quantity; it is dark, smoky or reddish brown and contains blood, albumin and casts. Uremic manifestations accompany these signs. Modern chemistry has added to these items the retention of nitrogenous wastes in the blood. Pathologists of that period were in agreement on the gross and microscopic changes in the kidneys after death from this condition. In examinations of tissues from some 200 cases of this syndrome, I have found no important item omitted from the pathologic description given by Adami[13] in 1909.

This form of renal disorder is not discussed in recent treatises on medicine, surgery or pathology. Its importance would justify an entire symposium, but time permits only a summary of it here. Those interested in details are referred to observations already published.[14] This renal syndrome has been recognized in more than 40 distinct clinical conditions; in many instances the authors stated that they were dealing with shock or with anoxia.

The clinical features are oliguria or anuria in a patient gravely ill from some condition independent of pre-existing renal disease; erythrocytes, albumin, casts, desquamated cells and debris in the urine; and progressive retention of nitrogenous wastes, leading to the syndrome of uremia.

The pathologic changes in the kidneys are as described by Adami.[13] The kidneys are enlarged, the cortex is swollen, edematous and pale in contrast to the deep red medulla. Petechial hemorrhages occur in the pelvic lining and within the substance of the kidney. Microscopically, the cells of the tubules are swollen, granular or vacuolated; often they have desquamated from the basement membrane. The lumina contain hyaline or granular casts, red cells, droplets of albumin and debris. Bowman's capsule often contains blood cells and albuminous material.

The description given by Lucké[15] corresponds with that given by others except in one particular: He found the degeneration and

necrosis sharply limited to the *lower* segment of the convoluted tubules, while others have found *both upper* and *lower* segments extensively involved. Hence his designation of this condition as "lower nephron nephrosis" is perhaps a misnomer. Either "acute tubular nephrosis" or "hemoglobinuric nephrosis" accurately designates this condition and is not misleading.

Attention is now invited to two instances of sublethal shock terminating in uremia from acute tubular nephrosis.

Resection of a rectal carcinoma, performed on a man aged 59 under spinal anesthesia, "was followed by shock from which he did not entirely recover." Transfusions of blood and of plasma did not restore the circulation; the systolic blood pressure fluctuated between 60 and 100. Urination was suppressed, the non-protein nitrogen rose progressively, and death occurred on the fourth post-operative day. The surgeon's diagnosis was "uremia secondary to severe post-operative shock."

The kidneys weighed 210 and 190 gm.; they conformed in every particular to the description given above. The tubular degeneration, vacuolization and necrosis involved chiefly the *upper* segments of the tubules where they adjoined Bowman's capsule.

In aviation at high altitudes, shock often develops even though oxygen is adequately supplied. "The most dangerous aspects are seen after a latent period of one to six hours, resulting in a full-blown vicious circle of peripheral circulatory insufficiency, tissue anoxia and hemoconcentration."[16] It has been my privilege to study five such cases. The following is a typical example:

A cadet was undergoing tests in a low-pressure chamber at a relative altitude of 38,000 feet when pains and distress developed. After gradual recompression, he was drowsy and incoherent, the pulse rate was 80 and the blood pressure 100/80. Severe circulatory deficiency developed four hours later; the pulse could not be felt; the hematocrit reading was 64.9; the patient was sweating and in profound shock. He was given plasma and fluids intravenously, and oxygen by inhalation but the circulatory deficiency was not relieved. The urine was scanty, highly colored, containing blood cells, pigmented casts and four-plus albumin. No blood chemical tests were made. He died 45 hours after removal from the low-pressure chamber.

The characteristic pattern of changes seen after shock were found at necropsy. The renal changes were identical with those found after

sublethal shock from diverse other causes. Again in this instance, the tubular degeneration and necrosis were most marked in the upper segments of the tubules.

How shock may be caused by low barometric pressure as encountered in high altitude aviation has not yet been determined. Obviously it is not due to trauma, intoxication nor infection, nor to any agent known to induce shock under such circumstances. Systemic anoxia is the one common denominator in this and in shock from other causes. The kidneys are known to be delicately susceptible to low oxygen tension. I tentatively ascribe the renal effects of shock, both from high altitude aviation and from other causes, to systemic anoxia resulting from circulatory deficiency.

Summary

Anoxia may develop from many unrelated conditions which reduce below physiologic levels the supply of oxygen to the tissues. The effects of this are similar, regardless of how the lack of oxygen originated.

Anoxia not only reduces metabolism, enzymatic action and other physiologic functions; it gravely impairs fluid balance by its effects on endothelium. These effects lead also to circulatory failure by causing atony, dilatation, and abnormal permeability of capillary walls.

Anoxia is one of the chief factors in the dynamics of secondary shock. It tends to establish a vicious circle leading to irreversible circulatory deficiency.

Anoxia is a major factor in the grave renal deficiency known as acute tubular nephrosis which develops in diverse forms of severe systemic disease.

Many pathologists believe that anoxia is the terminal factor in deaths from so-called natural causes. "It not only stops the machine, it wrecks the machinery."

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THE TREATMENT OF ANOXIA IN CLINICAL MEDICINE

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THE modern treatment of anoxia in clinical medicine appears to have been launched during the first World War by Haldane,[1] who administered oxygen to men in combat suffering from pulmonary edema due to irritant gas poisoning. Shortly after, Meakins[2] in England, and Stadie[3] and Barach[4] in the United States, showed that inhalation of 40 to 60 per cent oxygen in patients with pneumonia resulted in an increase of the arterial oxygen saturation to or near the normal level, with accompanying clinical improvement, decrease in pulse rate, clearing of cyanosis and alleviation of dyspnea. These findings were confirmed by Binger,[5] Boothby[6] and others. The demonstration that inhalation of oxygen was responsible for the prolongation of life in severe anoxic pneumonia was made by removal of patients still manifesting extensive disease from a tent or chamber containing 50 per cent oxygen; serious cardiorespiratory failure took place which could be remedied only by return to the oxygen-enriched atmosphere.[7] Although the inhalation of 50 per cent oxygen was shown repeatedly to be the specific factor which maintained life until the signs of the disease diminished, providing an additional chance for recovery, the skepticism concerning oxygen

treatment at that time was widespread and well-intrenched. The history of the early development of inhalational therapy must be found elsewhere,[1,8] but the early views and practices may be indicated by Hewlett's remarks in 1914:[9] "After an experience of thirty years with the open-air treatment of pneumonia I have come to the following conclusions: It should be used in all forms of pneumonia. . . . Finally, when cyanosis develops oxygen inhalations should be used. A funnel is attached to the rubber tubing coming from the oxygen tank, and this is held about an inch from the child's face." No mention was made as to how much oxygen should be bubbled from this low pressure tank, but in our observations in 1920 the concentration of oxygen inspired was about 25 per cent.

It is little wonder that there was a good deal of unwillingness to use the oxygen tent until the terminal stage had set in. In fact, my friends at Presbyterian Hospital used to say, "The only difference the oxygen tent makes is that patients die pink instead of blue." This opinion persisted until an opportunity to treat patients earlier in their disease was provided, when it became established that respiratory function was generally effectively maintained by inhalation of 50 per cent oxygen, and that the mortality in cyanotic cases of pneumonia was less when the patients were treated with oxygen instead of room air or open air.

Some years after it had been shown that pneumonia patients from whom oxygen had been withdrawn manifested signs of respiratory and circulatory failure, a similar study indicated the crucial value of oxygen in coronary thrombosis.[10,11]

Previously Keefer and Resnik[12] and Rizer[13] and others had indicated the important role of anoxia in the production of pain due to ischemia of the coronary circulation. Later, Boland[14] showed that 100 per cent oxygen relieved precordial pain due to coronary insufficiency when oxygen in concentrations of 50 per cent was relatively much less effective. In fact, it now appears that inhalation of oxygen in cases of coronary sclerosis diminishes the frequency and severity of anginal seizures,[15] even when administered for one-half hour two to three times daily.[16]

Investigation of the effects of inhalation of oxygen in concentrations of 50 per cent in patients with congestive heart failure showed that compensation could be established in certain cases, especially in those with arteriosclerosis, hypertensive vascular disease and coronary arteri-

osclerosis, when other routine measures had been found relatively ineffective. The results in myocardial failure associated with rheumatic carditis revealed that improvement was generally temporary in these cases, although at times life-saving in acute cardiac insufficiency. The clinical value of oxygen therapy was correlated with the physiological side effects of relief of dyspnea, such as decreased volume of breathing and an increased output of chlorides, which accompanied the diuresis in these patients.[17,18]

Studies on the clinical value of oxygen in pulmonary emphysema and fibrosis also brought out the correlation between the decrease in pulmonary ventilation and the increase in arterial carbon dioxide content.[19,20,21] The paper of Dr. Richards on congestive failure will present the results and effects of oxygen in these conditions. Anoxia in congestive failure and pulmonary emphysema was shown to be of crucial importance in maintaining dyspnea, even in cases in which the arterial oxygen saturation was lowered to a slight extent, i.e., between 90 and 93 per cent. The slight response of the chemoreceptors to this degree of anoxia in normal individuals cannot be used to explain the dyspnea of patients, since there is a marked difference in the response of patients and normal subjects both to anoxia and to inhalation of oxygen. This response to oxygen treatment requires special consideration.

The normal individual responds to inhalation of 100 per cent oxygen with an initial *increase* of pulmonary ventilation of 5 to 10 per cent. However, patients with congestive failure and pulmonary emphysema, in whom an arterial oxygen saturation of 90 to 95 per cent may be found, generally respond to inhalation of oxygen with a decrease in minute volume of respiration of 10 to 30 per cent. Furthermore, continued inhalation of oxygen-enriched atmosphere results in progressive relief of dyspnea despite a normal or nearly normal arterial oxygen saturation. The sensitivity of the chemoreceptors in patients with clinical dyspnea is evidently decidedly different from that of normal human beings.[8,21,22] Furthermore, undue emphasis has been placed, in the author's opinion, on reflexes from the bronchi and lungs; they play an important role, but by no means as exclusive a one as has been frequently stated by the advocates of the reflex cause of dyspnea, who have, on improper theoretical grounds, excluded anoxia as a significant factor. In addition, the arterial oxygen saturations may be found to be normal at times simply as a result of the hyperventilation that so often

accompanies the drawing of arterial blood in patients, which results in a fictitiously higher saturation than would be present under actual basal conditions.

In clinical practice, patients with pulmonary emphysema have been repeatedly observed who maintain a burdensome pulmonary ventilation, with the result that the arterial blood is almost normally saturated with oxygen. Similarly, patients with congestive failure, in addition to stagnant anoxia due to a decreased cardiac output, may manifest only a slight lowering of the arterial oxygen saturation. In both groups, the dyspnea is often markedly relieved after one or two days of breathing 50 per cent oxygen, even though the degree of pulmonary congestion is not decreased, as demonstrated by the fact that there is no change in the vital capacity. Since the reduction in pulmonary ventilation as a result of inhalation of oxygen is frequently between 15 and 30 per cent, the anoxic factor is evidently of considerable importance in these types of clinical dyspnea, and cannot be excluded by reports of a normal or nearly normal arterial oxygen saturation unless it has been shown that oxygen inhalation, comfortably and properly administered, is ineffective in reducing the volume of breathing. The chemoreceptors of the carotid sinus play a more significant role in clinical dyspnea than in normal respiration, in part because the increment in pulmonary ventilation due to anoxia constitutes a far larger proportion of the maximal breathing capacity in these patients than in normal human beings.

Despite careful attempts to analyze the components in clinical dyspnea by the functional tests now in use, it is frequently difficult to separate the effect of chemical stimuli from those originating in the proprioceptive sense organs of the lungs and the chest wall. To regard the chemical factor as relatively unimportant in cardiac dyspnea associated with passive pulmonary congestion (Harrison et al.[23,24]), or in pulmonary emphysema and fibrosis (Baldwin et al.[25]), simply on the basis of a normal or nearly normal oxygen saturation does not appear to be a justifiable assumption in many cases, since inhalation of oxygen results generally in a significant reduction in the volume of breathing and in elimination of dyspnea.[17-22]

As is well known, an increase in the requirements for oxygen that produces in normal human beings a moderate increase in pulmonary ventilation may initiate severe dyspnea in patients with chronic pulmon-

ary disease. In these cases, in which inhalation of oxygen is followed by a decrease in the volume of breathing and a resultant increase in the carbon dioxide content of arterial blood, the increase in CO_2 percentage in the expired air has the function of a homeostatic mechanism, making possible a greater elimination of carbon dioxide per liter of ventilation. Oxygen therapy, if the concentration of oxygen in the inspired air is increased gradually, is followed by a gradual rise in arterial CO_2 tension, an increase in the elimination of chlorides, retention of base and little or no change of pH. However, sudden exposure to high concentration of oxygen in patients who have been previously anoxic produces an acid shift in the acid base equilibrium, with irrationality, delirium or coma. These symptoms have not been observed by the author during regulated administration of oxygen.[8,21] In fact, patients have been observed in whom the arterial CO_2 content rose to 100 and 132 volumes per cent during a course of oxygen treatment, with a normal pH, relief of dyspnea, normal mental functioning. The CO_2 tension does not appear to be the significant factor in stimulating breathing or in producing adverse mental reactions *unless* it is associated with an acid shift in pH. However, acidosis produced by ammonium chloride does not result in mental symptoms, even when the breathing is markedly stimulated. The sudden change in brain oxygen tension is a manifest important factor; there are probably other chemical changes that play a role as yet not clear but dependent on the sudden change in oxygen tension. Even in patients with cerebral arteriosclerosis in whom inhalation of 50 per cent oxygen produces irrational, delirious states, a program of gradually increased oxygen concentrations in the inspired air results in no disturbance in mental function.[26]

In summary, then, the increased CO_2 tension in the arterial and alveolar air which follows the progressive decrease in pulmonary ventilation due to oxygen therapy may function in a homeostatic manner, since it results in a greater elimination of carbon dioxide per unit volume of breathing and in that way actually makes possible the relief of dyspnea initiated by the effect of oxygen on the carotid sinus. A respiratory acidosis is thus prevented by exhaling CO_2 in relatively high concentrations, as well as by retention of base and excretion of chlorides.

The use of oxygen in pulmonary emphysema has been emphasized as a therapy that requires expert management to avoid unfavorable reactions. The most practical method of obtaining the objective of

graded increase in oxygen concentration is to use the nasal catheter, or double bent nasal rubber tubes, at a flow of 1 liter of oxygen per minute for the first two days. An increase of 1 liter per minute every other day or every two days until a flow of 7 liters per minute is given. This is generally a safe technique of exposing the brain to an unaccustomed although normal oxygen tension. If desired, an oxygen tent may then be employed with a flow of 10 to 12 liters per minute for a period of one week to two weeks more. The oxygen concentration is then gradually lowered by resorting to the nasal catheter with a flow of 7 liters per minute and diminishing the flow by 1 liter every other day until the patient is no longer inhaling oxygen continuously. At this time, oxygen may be abandoned, or, in suitable cases, 70 per cent may be inhaled for twenty minutes two or three times a day.

Comroe[27] has also reported mental and physical depression with acidosis as a result of the use of oxygen in certain patients with pulmonary emphysema, but no graded program of oxygen administration was carried out in his cases. This consequence of sudden exposure to 40 to 50 per cent oxygen may be difficult to avoid in patients with pulmonary emphysema who suffer from acute oxygen want and dyspnea superimposed on a state of chronic pre-existing anoxia. The severity of impairment of respiratory function requires the use of increased oxygen concentrations, even at the peril of a respiratory acidosis. Some form of artificial respiration or intermittent pressure breathing may be required to wash out the carbon dioxide that might otherwise accumulate to serious proportions. In a patient recently observed by McCune and the author,[28] a respiratory acidosis was observed during the course of oxygen treatment of a child of three who suffered from asthma, pulmonary emphysema and edema of the lungs. Inhalation of 70 per cent oxygen was necessary to prevent anoxia. During treatment a pH of 7.1 was observed, with a characteristic decrease in serum chlorides. The intravenous injection of sodium lactate in this patient was followed by clinical improvement and an increase in pH to 7.25 and later to 7.46. It appeared likely that the recovery of the patient was aided by the restoration of a normal acid-base equilibrium. In two patients with shallow breathing treated with 80 per cent oxygen by the author in 1920, a marked increase in CO_2 content of the arterial blood, from 60 to 88 volumes per cent, took place in one-and-one-half hours.[4] The existence of a respiratory acidosis of 7.22 was demonstrated in one case before treatment. From

these observations, it would appear desirable to test the carbon dioxide content and pH in cases in which the pulmonary ventilation was markedly lowered as a result of oxygen therapy, such as in respiratory paralysis occurring in poliomyelitis.

Oxygen is employed in a variety of clinical disturbances of respiratory function, especially in the treatment of bronchial asthma during a program of bronchial relaxation. Since a remission is more apt to take place when bronchodilator drugs to which the patient has become refractory are curtailed, inhalational therapy in this situation prevents increasing anoxia. In this disease the inhalation of helium with oxygen is used for severe cases or as an adjuvant in the program of remissive therapy. The introduction of helium as a substitute for nitrogen was based on the lower specific gravity of helium as contrasted to either oxygen or nitrogen. A mixture of 20 per cent oxygen with 80 per cent helium has a weight 1/3 that of a comparable volume of oxygen and is passed through constricted orifices at a pressure almost one-half that required for oxygen.[29, 30]

As an additional method of providing oxygen with a decreased effort, both oxygen and helium-oxygen mixtures have been administered under continuous positive pressure.[31, 32] The presence of a pressure of 3 to 10 cm. of water during inspiration aids the entrance of oxygen in the lungs during this cycle by gentle pressure inward of the atmosphere, decreasing therefore the pathologically elevated negative pressure produced during inspiration by obstructive dyspnea;[33] during the expiratory cycle a wider lumen of the bronchial passageway aids the elimination of air from the lungs.[34] Pressure breathing with oxygen is used not only in obstructive dyspnea but also in edema of the lungs in which the retarding of blood entering the right side of the heart permits the organ to work on a small volume of blood, especially in left ventricular failure. In cases in which the pulmonary edema is due to increased permeability of the pulmonary capillaries, a direct physical pressure of one-half the applied pressure tends to counteract the hydrostatic pressure in the pulmonary capillaries and to prevent oozing of serum into the alveoli.

Pressure breathing has been found effective in the treatment of acute pulmonary edema of various types, not only when the pressure is exerted continuously during inspiration and expiration but also when it is present intermittently in either cycle of breathing. The simplest clinical method of administration consists of its use during expiration, either against the

pressure maintained by a water bottle or through constricted orifices.[35] A number of reports have made manifest its value in this clinical entity.[36, 37] Positive pressure has also been employed in intermittent form when the height of pressure was during inspiration, with the pressure either gradually or precipitously falling during expiration.[38, 39, 40, 41] Many studies have been carried out on the effects on the circulation of pressure breathing. A recent review of the pressure employed in aviation medicine suggested that the effect on cardiac output was proportional to the mean pressure, whether administered by a continuous pressure breathing or an intermittent pressure breathing device.[40]

Many other studies on applied respiratory physiology, including a mechanism which sustains life without breathing, that cannot be adequately reviewed,[41-51] have included various types of physiologically directed therapy. However, a recent suggestion in the treatment of a serious form of ischemic anoxia merits special attention.

Inhalation of oxygen-enriched atmospheres may be of critical help in ischemic anoxia, not only because of the rise in the hemoglobin oxygen saturation but as a result of the six-fold increase in physically dissolved oxygen (when 100 per cent oxygen is given), which is delivered to the partially obstructed artery as well as to the collateral vessels. With a 10 per cent increase in oxygen content of each unit of circulating arterial blood, a substantially higher pressure of oxygen is present in the capillaries. Thus, in experimental hemorrhagic shock, inhalation of 100 per cent oxygen resulted in an increase in venous oxygen saturation from 20 to 33 per cent and an elevation of the partial pressure of oxygen from 14 to 21 mm. Hg.

The relief of cardiac pain and coronary insufficiency, in cases of coronary thrombosis treated by oxygen, is a good illustration of the importance of increase in physically dissolved oxygen, and was in fact the stimulus for the use of oxygen in the treatment of cerebral embolus and thrombosis, originally suggested by Poulton, [48] who found in a small series of cases that the end results in oxygen-treated cases appeared to indicate less brain damage than might have been expected. Although the clinical evidence at hand is at present insufficient to demonstrate the value of oxygen treatment in these conditions, the known sensitivity of the brain to anoxia, plus the fact that a marked increase in physically dissolved oxygen can be obtained, constitute a sound physiologic argument for continuous residence in an atmosphere of 50 to 70 per cent

oxygen during the first week following cerebral thrombosis.

The consequences of brain ischemia in cerebral arteriosclerosis would appear to offer an interesting field of research from the standpoint of measures that might be employed to prevent the accumulation of products of insufficient oxidation, such as inhalation of oxygen and the use of drugs that result in a dilation of blood vessels in the brain. Since an abrupt exposure to inhalation of 50 per cent oxygen to patients with cerebral arteriosclerosis frequently results in delirium or coma, as has been observed following a similar type of treatment of patients with anoxic pulmonary emphysema, a gradual increase in the oxygen concentration of the inspired atmosphere should also be employed in these patients. A study of brain anoxia and its treatment in senescence would appear to be eminently justified.

The methods of administering therapeutic gases and various types of pressure breathing have undergone a progressive development during the past three decades with improvement in efficiency of operation and in the provision of increased comfort to the patient.[8, 49-51] Specialized training of technicians would appear to be highly desirable to carry out the myriad procedures in inhalational therapy, for only through skilled attention can the purpose for which the treatment of anoxia in clinical medicine was intended be ultimately accomplished.

Discussion

Many omissions have been necessary in the attempt to cover a subject as extensive as that of the treatment of anoxia in clinical medicine. Since it has been my privilege for the past thirty years to have been occupied by various aspects of impairment of respiratory function and the application of presumably appropriate therapeutic procedures, I have, I hope quite naturally, called to mind especially the experiences which my colleagues and I have had in this field. The many studies that dealt with anoxia in shock, asphyxial states, anesthesia, respiratory paralysis, atelectasis of the lungs of the new-born and other clinical entities characterized by oxygen-want were not considered less important, but because these conditions were to be presented in this symposium by those with more special knowledge and training, I have not discussed them.

The position and lack-of-position of this department of medicine warrants a brief comment. The importance of the treatment of anoxia is now universally acknowledged in a way that was not comprehended at

the beginning of the century; however, the lack-of-position of the special province of inhalational therapy is revealed by the very small amount of teaching time allotted to it in medical school curricula. Furthermore, the subject of respiratory physiology, as currently presented, does not encompass the principles of actual treatment of impairment of respiratory function. The pressure breathing mask, for example, may be prescribed for the treatment of pulmonary edema or obstructive dyspnea without the student's being aware of the effects of pressure breathing on intrapleural pressures, bronchial wall diameter, alveolar ventilation, serous exudation from pulmonary capillaries, cardiac output or other alterations of the mechanics of breathing.

A top-heavy attention to apparatus, in contrast to the purpose for which it is intended, has had at times unfortunate consequences. An illustration of this situation is the administration of oxygen by devices which permit harmful concentrations of carbon dioxide. When a mask with a rebreathing bag is employed at oxygen flows of 3 to 6 liters per minute (such as the B.L.B.), the inspired air may contain 1.5 to 2.5 per cent carbon dioxide, which may result in a serious increase in dyspnea in patients with cardiorespiratory disease. If an oxygen tent is employed with too little leakage of air and too low oxygen flows, carbon dioxide accumulates to excessive proportions. The average adult gives off approximately 250 cc. of carbon dioxide per minute; it is obvious that 25 liters of oxygen and air must enter the tent per minute to result in a concentration of 1 per cent CO_2 in the inhaled atmosphere. A tent that maintains 50 per cent oxygen with a flow of 8 liters per minute of oxygen is not operating satisfactorily, since the carbon dioxide concentration must necessarily be above 1 per cent. Many illustrations of this nature could be cited, in which a lack of understanding of both the principle and the techniques of inhalational therapy were responsible for the so-called failure of oxygen treatment to relieve dyspnea of cardiac and respiratory insufficiency.

The intelligent use of the various procedures now employed to improve respiratory function seems to me to require more specialized teaching than prevails at present in most medical schools.

Summary

The use of 40 to 60 per cent concentrations of oxygen in clinical medicine began three decades ago with the treatment of pneumonia. A

significant increase in the arterial oxygen saturation of anoxic patients was correlated with signs of clinical improvement. Prior to that time the prevailing therapeutic program consisted of the so-called open air treatment. When severe cyanosis developed as a terminal state, inhalation of oxygen was administered through a funnel placed an inch or two from the patient's face. That effective oxygen therapy at times prolonged life was demonstrated when patients with extensive disease removed from a tent containing 50 per cent oxygen suffered cardiorespiratory failure which was later alleviated by return to the oxygen-enriched atmosphere. The death rate in cases of cyanotic pneumonia treated with oxygen was finally shown to be less than in comparable series not treated with oxygen.

The results of the employment of 30 to 50 per cent oxygen in hypertrophic pulmonary emphysema indicated that considerable restoration of respiratory function may take place by careful regulation of the concentration of oxygen administered. An increased elimination of carbon dioxide per breath may function as an advantageous homeostatic mechanism when oxygen is given in gradually increasing concentrations. Respiratory acidosis may be produced when high concentrations of oxygen are given to patients with severe anoxia; the indication for 50 per cent oxygen for the treatment of acute respiratory or cardiac insufficiency in these patients constitutes a difficult and complex problem in management.

The substitution of helium for nitrogen in air was based on the low molecular weight of helium. A mixture of 80 per cent helium with 20 per cent oxygen was delivered through a constricted orifice at a pressure 40 per cent less than that required for oxygen.

Pressure breathing was employed for the administration of helium-oxygen mixtures and oxygen-enriched air, in patients with bronchial asthma and obstructive dyspnea. The entrance of oxygen into the lungs was aided by positive pressure during the inspiratory cycle, which resulted in a lowering of the pathologically elevated negative intrapleural pressure. A wider or more patent bronchial passageway was produced by pressure in expiration.

Pressure breathing has been used for the treatment of edema of the lungs, occurring either as a result of left ventricular failure or as a consequence of increase in permeability of the pulmonary capillaries, as in pneumonia or irritant gas poisoning. In these conditions pressure breath-

ing of the intermittent type has also been found useful, with maximum pressure produced either in expiration or inspiration.

The inhalation of 50 per cent and at times higher concentrations of oxygen has been found to be of special value in the treatment of coronary thrombosis and congestive heart failure. Patients who have had an acute occlusion of the coronary artery, suffering from precordial pain, heart failure and shock, have frequently been critically improved by inhalation of oxygen-enriched atmospheres. The employment of oxygen continuously in patients with congestive cardiac failure was also shown to be followed by relief of shortness of breath, and, in some cases, by an increased output of urine and clearing of edema.

A recent interesting suggestion is the treatment of cerebral anoxia due to cerebral thrombosis, embolism or hemorrhage by inhalation of 50 to 70 per cent oxygen. Although the number of cases so far reported is small, the theoretical evidence on which this proposal was made seems sufficiently sound as to indicate its further trial.

Inadequate supervision of the methods of application of therapeutic gases and pressures has recently been revealed as a widespread and serious problem in medical care. The remedy for this situation must ultimately be shouldered by those in charge of teaching in the medical schools. The medical student who is not formally instructed in both the principles and techniques of treatment of the complex anoxic emergencies in clinical medicine is dependent on his interneship to provide this specialized knowledge and training. Unfortunately, few hospitals are equipped to carry out modern methods of inhalational therapy, or have a department head available for teaching. Formal instruction would appear to be desirable since the range of treatment of impairment of respiratory function has extended considerably during the past three decades.

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*INHALATIONAL THERAPY IN CARDIAC DISEASES**

CARDIAC FAILURE

DICKINSON WOODRUFF RICHARDS, JR.

INHALATIONAL therapy in cardiac failure is primarily oxygen therapy. The chief indications for this form of treatment in cardiac conditions, the physiological principles upon which it is based, and the measurement of its effects were worked out fairly completely some fifteen or twenty years ago. Since that time there has been steady if not spectacular progress, due to advances in several different fields of clinical investigation. Perhaps the most important have been the improvements in apparatus and technique, in great part the work of Dr. Alvan L. Barach and his associates.[1] Much practical experience over almost two decades has determined how inhalational therapy can be given, and what can and what cannot be expected from it. Further insight into the principles of oxygen therapy has been gained through the extensive researches on anoxia carried out during the recent war. New methods of measuring cardiac and circulatory functions have more clearly defined the nature of the disturbances in the various different forms of chronic cardiac disease.

Against this background of added knowledge, inhalational therapy can now be more rationally applied, and its indications and contraindications better understood.

In this paper I shall present some of these newer aspects of inhalational treatment in certain forms of cardiac failure.

For present purposes, cardiac failure may be divided into three groups: 1) that secondary to coronary artery disease with myocardial infarction; 2) left-sided or combined right-sided and left-sided congestive heart failure due to intrinsic myocardial or valvular heart disease; and 3) cor pulmonale.

The first of these is discussed by Dr. Robert Levy in this symposium;

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I shall attempt to cover in brief outline the other two.

Since the administration of oxygen is by far the most important form of inhalational therapy in heart disease, I shall consider this first, and mention other forms, such as positive pressure and bronchodilators, only in passing.

At the risk of unnecessary repetition of familiar facts, I should like first to review briefly the clinical indications for oxygen therapy, and the physiological effects that oxygen will produce in patients suffering from myocardial or valvular heart disease in congestive failure.

The clinical indications are: 1) Dyspnea, with or without orthopnea 2) Restlessness. 3) Cyanosis. 4) Cardiac pain. 5) Cough.

1. *Dyspnea*, in its various forms, is the first indication for oxygen therapy. The dyspnea of congestive heart failure is caused in part by the decreased breathing capacity of the engorged, inelastic, sometimes edematous lung, and in part by a much increased actual ventilation, stimulated by anoxia, and perhaps by reflex influences. In cardiac asthma obstruction of the air passages may be an added factor. Correspondingly, relief of dyspnea by oxygen is the best index of its therapeutic effect.

2. *Restlessness.* By this term I refer actually to a whole train or sequence of mental states. The exhaustive studies of low-oxygen pressure during the war brought out clearly the many mental and nervous aspects of anoxia, ranging from slight depressions of intellectual acuity through restlessness, insomnia, and the like, to profound mental aberrations, disorientation, and coma. Clinicians often fail to appreciate, however, how these same symptoms may occur in the cerebral anoxia of heart failure.

3. *Cyanosis.* In the forms of congestive heart failure which we are now considering, blood flow or cardiac output is decreased. This means that oxygen in the venous blood is low, producing the so-called stagnant anoxia. In addition there may be some degree of arterial oxygen unsaturation due to inadequate aeration of the blood in the congested lung. Clinically, it is helpful, when possible, to take a sample of arterial blood and measure its oxygen saturation.

4. *Cardiac pain.* Anoxia as a factor in cardiac pain concerns chiefly coronary heart disease, and need not be further considered in the present discussion.

5. *Cough* may be an important, occasionally a dominant, manifestation of pulmonary congestion, aggravated by dyspnea and restlessness.

How should oxygen therapy be administered in congestive heart failure? This is obviously not the place to give full details of procedure. At the same time technical advances in recent years have been important, and many physicians are unfamiliar with them.

For severe left ventricular failure with dyspnea and orthopnea at rest, the oxygen tent is best. With the usual care to prevent leakage, and with an oxygen inflow from the tank of 8 to 10 liters per minute, oxygen concentration within the tent can be maintained at about 40 to 45 per cent. With very special efforts to keep the tent closed, and the oxygen inflow around 15 to 20 liters per minute, 50 per cent oxygen concentration can be achieved. For most patients with congestive heart failure from 40 to 45 per cent oxygen is sufficient to relieve dyspnea and anoxia. With severe myocardial infarction in shock, and in many cases of cor pulmonale, the higher oxygen concentrations provided by the mask may be needed. I shall consider this latter problem later. The tent has the obvious advantages of providing continuous high oxygen atmosphere, plus cooling, of avoiding the use of uncomfortable apparatus around the nose and mouth, and of permitting the patient to cough and raise sputum, talk, eat, and drink.

How long should oxygen therapy be continued in acute decompensation? It is of course difficult to make rules, since all depends on the patient's response, but in general it is advisable, if the degree of failure is severe and has been prolonged, to maintain continuous oxygen therapy for two or three days after symptoms of acute failure have subsided, then give oxygen intermittently, using the tent, mask, or catheter at intervals during the day and throughout the night, for an additional two to seven days.

For milder degrees of congestive failure, the meter mask, with oxygen concentration set at about 40 per cent, or the intranasal catheter, or the double metal nasal catheter with apertures just within the nostrils, may be used. The catheter techniques have somewhat passed out of fashion, but are simple and effective when oxygen concentrations around 35 per cent are sufficient to control symptoms. Some patients of course do not tolerate the intranasal catheter even when used carefully, with the oxygen well humidified by passage through a water bottle, and the catheter changed several times each twenty-four hours. I might note that in our experience it is preferable to keep the tip of the catheter in the nasopharynx rather than lower, in the oropharynx,

as the latter position is more irritating and may result in dysphagia, or air swallowing.

Is there any place for carbon dioxide in the inhalational therapy of heart failure? The answer to this is a categorical no. The respiratory stimulus is already increased; any concentration of carbon dioxide in the inhaled air increases respiration and dyspnea and is therefore undesirable. Actually, every effort should be made to prevent the accumulation of carbon dioxide in all inhalational therapy apparatus.

Is positive pressure useful in the treatment of congestive heart failure? This is a somewhat controversial subject. It has been our experience, however, that in acute left ventricular failure with pulmonary congestion and pulmonary edema, the use of expiratory positive pressure for a few hours has resulted in a decrease in pulmonary rales and corresponding clinical benefit. The most convenient apparatus is a well fitting mask providing positive pressure expiration through an adjustable narrowed orifice.

There is also some experimental evidence indicating that positive pressure may improve the circulation in congestive failure. Motley, Cournand, et al[2] found that the damming back of venous return to the chest and heart produced by positive pressure breathing resulted in a decrease in cardiac output in normal subjects, but an increase in cardiac output in some cases of congestive heart failure. The positive pressure apparently prevented an excessive venous return, thus acting in a manner similar to tourniquets on the limbs, or phlebotomy.

I should like to conclude this discussion of oxygen therapy in congestive myocardial failure with a brief review of the actual physiological changes that take place progressively as a patient recovers compensation in a high oxygen atmosphere.

Figure 1, taken from a paper published some years ago,[3] gives the typical sequence of events. The patient was a man of 56 with arteriosclerotic heart disease in severe left-sided and right-sided congestive failure.

When the oxygen concentration was raised to 45 per cent, there was an almost immediate rise in arterial oxygen concentration from 86 per cent to 98 per cent. This was accompanied by progressive clearing of cyanosis, decrease in pulmonary ventilation, and relief of dyspnea. It should be noted that dyspnea is also regularly relieved by a high oxygen atmosphere even in patients in congestive failure whose arterial

oxygen concentrations are but little if at all reduced below the normal of 93 to 96 per cent. The small increments of arterial oxygen provided by the increase to 98 or 99 per cent saturation, associated as they are with considerable increases in blood oxygen tensions at these levels, apparently have a marked effect on the respiratory center. It may be also that these small increases affect heart muscle and result in increased cardiac output; but this has not yet been adequately measured.

At all events, the reduced pulmonary ventilation results in a rise in carbon dioxide levels in the blood, which continues for several days. This is a physiological adaptation and in these forms of heart failure is never harmful.

As compensation is further restored, urinary output of water and chloride increases, and in this case it proceeded to complete diuresis. The fall in blood carbon dioxide in the second week is an expected occurrence, associated with increased vital capacity and generally improved circulatory and ventilatory function. The patient was removed from the high oxygen atmosphere, as seen, after sixteen days and became ambulatory shortly afterward.

One last question about oxygen therapy in congestive heart failure secondary to intrinsic heart disease: is oxygen therapy ever harmful? I think it is safe to say that there are no physiological contraindications to the use of oxygen, even in high dosage, in this type of heart failure, beyond the fact that occasionally a chronically decompensated patient may become habituated to it, and discontinuance of oxygen may present a problem.

With cor pulmonale, which is the other form of cardiac failure that I should like to discuss, both the pathological physiology and the response to oxygen are totally different from those in congestive failure due to intrinsic cardiac disease, as very recent studies[4] have shown.

In the first place, the primary lesions in cor pulmonale are in the lungs, consisting usually of marked emphysema with large stagnant alveolar spaces, chronic or recurrent narrowing and obstruction of bronchial air passages, obstructive dyspnea, cyanosis with an arterial oxygen saturation sometimes down to 80 per cent or even 70 per cent or lower, increased blood carbon dioxide, and often polycythemia. The heart failure is on the right side secondary to markedly increased pulmonary artery pressures—a pulmonary arterial hypertension. When the congestive state develops, there will be right ventricular dilatation,

elevation of systemic venous pressure, greatly increased blood volume, congestion and edema of variable extent. The cardiac output, curiously enough, is apt to be increased well above normal, apparently compensatory to the anoxia.

In the treatment of these patients, oxygen is obviously necessary as an acute measure and it will usually bring striking and immediate relief. The concentration of oxygen needed will vary with the form and severity of the pulmonary insufficiency present. For the mild and moderate degrees of dyspnea and cyanosis, with but little obstructive component or asthma, a nasal catheter, a tent or a mask at low concentrations will be sufficient.

In more severe decompensation, and if dyspnea, cyanosis or restlessness persists with lower arterial oxygen concentrations, the use of the mask with concentrations up to 60 or 70 per cent for short periods may be necessary. Furthermore, it must always be kept in mind that with cor pulmonale oxygen supplies but one of the deficiencies in pulmonary function. Most patients have obstruction of the tracheobronchial air passages to a greater or less degree. There is no use administering oxygen if it does not reach the alveoli through adequate pulmonary ventilation. Observation of chest movements and auscultation of the lungs will often help to reveal the extent of bronchiolar obstruction. Oxygen therapy then should be interrupted by two to five minute periods of inhalation of bronchodilator drugs, vaporized from a pressure tank of air or oxygen, or by intravenous aminophyllin; following this the patient should be encouraged to cough and raise sputum. In extreme cases it may be necessary to clear the air passages by suction. Oxygen therapy in such cases may be best given with positive pressure, either expiratory or continuous.

In this type of case, it might be noted, the use of morphine is especially dangerous, as it decreases respiration and stops the cough reflex. Other aspects of therapy, such as digitalization, diuretics, and phlebotomy, are beyond the scope of this paper.

It is in this type of case, however, that prolonged oxygen therapy runs into its most serious contraindication—namely, the development of carbon dioxide narcosis. While this phenomenon has long been known, it has had little emphasis in the literature. It therefore deserves a careful description, and to this I should like to devote the remainder of the present discussion.

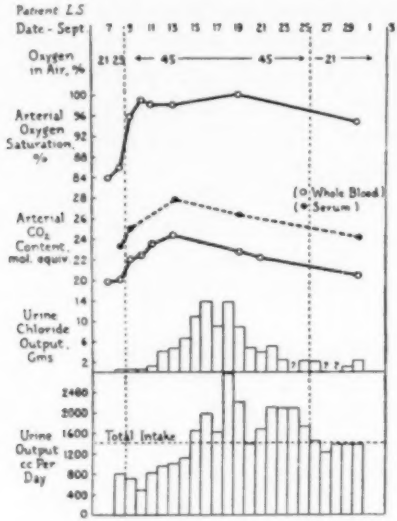

Fig. 1. Changes in respiratory gases and urinary excretion during high oxygen therapy. Patient with arteriosclerotic heart disease, in failure.*

In Figure 1, which shows the sequence of physiological events that take place during oxygen therapy in a case of congestive heart failure, there was a progressive rise in carbon dioxide level in the blood, over a period of four or five days, amounting in all to 8 to 10 volumes per cent, and caused by the relatively diminished pulmonary ventilation that is associated with the breathing of a high concentration of oxygen. Carbon dioxide is less adequately eliminated by the decreased ventilation. Or, to put the situation somewhat differently, it requires a higher concentration of carbon dioxide in each breath, when ventilation is less, in order to eliminate the body's CO_2 production and therefore the alveolar and the blood levels must be higher. This carbon dioxide increase consists in both a rise in CO_2 tension and an increase in blood bicarbonate. The increase in bicarbonate comes about through a selective and practically quantitative fall in plasma chloride.

When oxygen is given in chronic emphysema, in which pulmonary ventilation is already ineffectual because of obstructed stagnant air spaces and blood carbon dioxide is already high, the decrease in ventila-

* Reprinted by permission of the Clarendon Press, Oxford, from the Quarterly Journal of Med. Vol. 3, 1934, 427. D. W. Richards, Jr. and A. L. Barach.

TABLE I. RISE IN BLOOD CO_2 IN ANOXEMIC SUBJECTS DURING OXYGEN THERAPY

Subject	*Date*	*Oxygen*	*Arterial Blood*			
		% in air	O_2 sat'n %	Total CO_2 vols. %	pCO_2 mm.	pHs
C.M.	9/21/33	21	68	62.6	58.0	7.40
Pulmonary	9/28	Patient put in oxygen room				
fibrosis	10/2	50	94	90.1	89.0	7.38
	10/6	50	—	93.7	—	—
	10/19	50	93	91.7	100.0	7.32
	10/20	35	Oxygen tent.			
	11/6	21	82	69.9	54.0	7.46
	11/9	25	94	72.2	—	—
	12/5	25	85	66.8	—	—
F.S.	2/28/35	21	86	66.0	63.0	7.38
Pulmonary	2/28	Patient put in oxygen room				
fibrosis	2/28	45	98	66.9	67.9	7.35
	3/1	45	98	69.4	75.0	7.34
	3/4	45	97	78.5	85.0	7.34
	3/6	45	97	83.5	99.0	7.29
	3/8	45	96	84.2	94.0	7.31
	3/18	45	94	81.8	85.0	7.34
	3/23	45	97	80.9	81.5	7.36

tion caused by high oxygen further depresses the elimination of carbon dioxide and in the course of four or five days the blood level may rise excessively high, arterial CO_2 contents of 80, 90, or even 100 volumes per cent being not uncommon.

At these levels, the CO_2 tension in lungs and blood approaches 100 millimeters or about one-seventh of an atmosphere or about 14 per cent. At these concentrations, carbon dioxide has a true narcotic effect and this is what these patients show clinically. They become drowsy, stuporous, eventually comatose.

Table I shows the progressive changes in carbon dioxide content in two patients with chronic pulmonary disease and cor pulmonale, when treated with oxygen. As the CO_2 levels rose, they became drowsy, then confused and disoriented, finally stuporous, but recovered after oxygen was reduced.

This condition does not occur very frequently, perhaps in 10 per cent of severe cases of chronic emphysema with cor pulmonale treated intensively with oxygen. Any patient with chronic pulmonary disease,

however, in whom the blood CO_2 is definitely elevated before oxygen treatment, runs the chance of developing CO_2 narcosis during oxygen therapy.

The key to detection of this condition in its early stages is the CO_2 level of the blood. If this rises over 80 or 85 volumes per cent during oxygen therapy, an impending state of narcosis is to be suspected.

Can the condition be prevented or treated? It seems to be true clinically, as Barach has shown, that CO_2 narcosis is less likely to develop, in susceptible patients, if oxygen is administered in gradually increasing concentrations, taking perhaps a week to reach 50 per cent, rather than starting at once at very high concentrations in the inhaled air. Or, oxygen therapy may be given intermittently at first, rather than continuously.

There is also some theoretical basis for such procedures. The damage, in CO_2 narcosis, is caused by CO_2 as a gas; in other words, the level of carbonic acid, H_2CO_3 in the blood. Thus, the more acid the blood, the more severe the symptoms. Conversely, if bicarbonate—HCO_3—increases, with rise in blood pH, the less the symptoms will be. With a more gradual oxygen effect, the kidneys have time, so to speak, to readjust the body electrolytes so as to maintain or restore a normal blood pH. An example of this is seen in the figures of patient F.S., in Table I. Here, even with sustained oxygen inhalation of 45 per cent, there was a gradual decrease in CO_2 tension and rise in pH, though the total arterial whole blood CO_2 changed but little. With the decrease in CO_2 pressure, the symptoms of narcosis became less in this patient.

It must be recognized, however, that in extreme decompensation the therapeutic situation may become impossible: the patient cannot live without high oxygen inhalation, yet breathing a high concentration of oxygen precipitates coma from accumulation of carbon dioxide.

To summarize this aspect of the discussion, the treatment of cor pulmonale with right-side congestive failure has to be a combined effort to provide physiological relief both for the pulmonary and the cardiac dysfunctions. Figure 2, from a recent paper,[4] will perhaps bring together this argument by showing a case of advanced cor pulmonale studied by cardiac catheterization while in failure and again two and a half months later, after recovery of compensation. In failure cardiac output was increased, pulmonary arterial hypertension was marked, arterial oxygen saturation was very low, and venous pressure was high, with

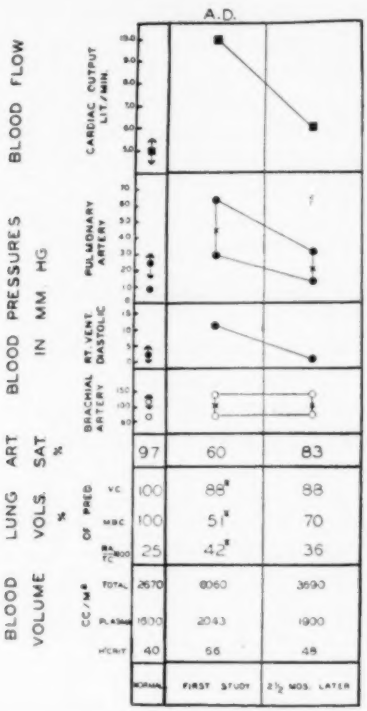

Fig. 2. Patient A.D., age 55, with long-standing bronchial asthma, chronic emphysema, cor pulmonale, Ayerza syndrome. Measurements of circulation while in congestive failure (left), and after compensation was restored (right).

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systemic congestion, polycythemia, and greatly increased blood volume. All these abnormalities returned toward normal with recovered compensation, and the treatment was directed to these ends: pulmonary function was aided by bronchodilators, expectorants and oxygen, and cardiocirculatory function by oxygen, digitalis, diuretics and frequent phlebotomies, the latter totalling some 1,500 cc.

In summary, I have attempted to outline in this discussion some of the physiological principles and practical details of inhalational therapy in congestive heart failure, and to emphasize the contrast between failure associated with intrinsic heart disease, and that encountered in cor pulmonale secondary to chronic pulmonary disease.

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OXYGEN IN CARDIAC INFARCTION*

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INFARCTION of the myocardium results from narrowing or occlusion of a coronary artery. The commonest cause of such pathologic changes is atherosclerosis; less frequently syphilis of the aorta produces similar effects when the disease involves one of the coronary orifices, or both. Coronary embolism is rarely responsible. The physiologic disturbances associated with cardiac ischemia vary according to three basic factors: 1) the size of the vessel involved; 2) the rate of closure; 3) the efficacy of the remainder of the coronary circulation in maintaining an adequate flow of blood through the heart muscle.

Obviously, the size of the infarct will depend in large measure on the calibre of the artery affected; a large area of infarction, as a rule, will result in more profound disorder than a small one. The location is of lesser importance. Gradual narrowing, with eventual closure, affords an opportunity for the development of a collateral bed so that the final shut-down is apt to be a less upsetting event. For this reason, occlusion in a patient who has suffered from anginal attacks for a number of years is often accompanied by milder symptoms than in one whose attack of coronary thrombosis is the first evidence of serious trouble. Finally, if atheromatosis in the arteries not immediately involved is slight or absent the myocardium receives enough blood to maintain function during the

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early critical period. In deciding on the advisability or necessity of using oxygen in treatment, an estimate of all of these factors must be made.

The symptoms and signs of cardiac infarction vary widely. The entire episode may be "silent" and discovered only in the course of later electrocardiographic examination; or it may be stormy and followed by evidences of shock. All intermediate grades of severity are observed.

The mechanism of shock following cardiac infarction differs from that seen after hemorrhage or trauma. In so-called "surgical shock," it is the peripheral circulation which basically is at fault. The cardiac output is diminished because of a decreased blood volume and a lowered venous return to the heart. In myocardial infarction, on the other hand, it is primarily the central pumping station that fails.[1] The left ventricle, which is predominantly the site of injury, is unable to eject a sufficient volume of blood to support an effective peripheral flow. The infarct, therefore, results not only in an area of anoxia in the myocardium but also in hypoxia of all the organs and tissues of the body. Passive congestion in the lungs impairs their function with respect to the absorption of oxygen, since the gas does not diffuse readily through edematous alveolar walls. Loss of pulmonary distensibility prevents adequate ventilation and the blood passing through the lungs is incompletely aerated. A vicious circle is initiated which does not tend to correct itself unless aid is given from without.

Indications for the Therapeutic Use of Oxygen

It is not necessary to administer oxygen to every patient with a cardiac infarct. But even though the clinical picture at the outset may appear to be mild, extension of a thrombus or the occurrence of pulmonary edema or an arrhythmia may cause sudden and grave changes. It is therefore desirable to have the required apparatus always readily available on short notice. To give oxygen when in doubt is far better than to withhold it until irreversible changes in the circulation have taken place.

Clinical criteria which indicate the need for oxygen therapy cannot be defined with scientific precision. But the usefulness of oxygen has been demonstrated in the following conditions:

1. Cyanosis.
2. Shock.
3. Severe and persistent cardiac pain.

4. Dyspnea.
5. Acute pulmonary edema.
6. Congestive failure.
7. Certain cardiac arrhythmias.
8. Rising heart rate.
9. Sharp fall in blood pressure.
10. Marked leukocytosis.
11. High fever.
12. Cheyne-Stokes respiration.

A bluish or purple color of the ears, lips and finger tips is a simple and graphic index of oxygen lack; any patient with *cyanosis* is a candidate for relief.

In *shock*, there is an ashen-grey tint to the skin, sometimes, but not always, accompanied by cyanosis. The face and body are bathed in clammy sweat. The extremities are cold. The sensorium may be clear and the patient is often apprehensive and restless. The heart rate is rapid; the blood pressure falls, often to levels below 90 mm. Hg systolic. At the onset, the temperature is normal or subnormal, rising, in the course of twenty-four hours, to fever heights.

Cardiac pain is frequently agonizing and is not relieved even by relatively large doses of opiates injected intravenously. If additional amounts are given, there is danger that vomiting may be induced. Discomfort is due to anoxemia of the heart muscle.

Dyspnea frequently is an early sign of left ventricular weakness and its prompt relief may avert more serious functional disorder, such as *acute pulmonary edema*. When frank *congestive failure* develops there is clear evidence that the damage to the myocardium has impaired the ability of the heart to eject amounts of blood adequate to sustain the circulation. Failure may be due, in part, to a deficient venous return to the heart. Better oxygenation of the blood, and particularly of the heart and kidneys, helps to tide the entire organism over the emergency and to restore circulatory balance.

The onset of certain *cardiac arrhythmias* places an added burden on the heart in maintaining its output. Chief among these are ventricular tachycardia, auriculoventricular heart block, and auricular fibrillation or flutter with rapid ventricular rate. Ventricular tachycardia may terminate in ventricular fibrillation and death. In heart block, Adams-Stokes attacks sometimes are most distressing and occasionally a long

period of asystole or ventricular fibrillation may prove fatal. Premature beats, particularly when they arise in the ventricles, are sometimes forerunners of fibrillation of these chambers.

A *rising heart rate* is a sign of a failing heart and perhaps should be classed as early evidence of cardiac insufficiency. A *sharp fall in blood pressure* often is part of the picture of shock, although it may appear independently of it.

A *high leukocyte count*, above 15,000 per cu.mm., indicates an infarct of large size. In fact, the degree of leukocytosis, in the absence of complications which might modify it, is one of the best early indexes of the severity of the initial lesion. It has been noted that a white cell count of over 25,000 per cu. mm. usually denotes a grave prognosis. Similarly, *high fever*, if due solely to the infarct, is a sign of serious cardiac damage. A rectal temperature over 104° F., like a leukocytosis above 25,000, is cause for concern.[2]

Periodic breathing of the Cheyne-Stokes variety is an expression of hypoxia of the respiratory center. The possible effect of morphine in depressing this center must always be kept in mind as a contributing factor.

These evidences of oxygen lack are all helpful guides; but the final decision as to whether oxygen should be given must be based on clinical experience and judgment.

Method and Technique of Administering Oxygen

The nasal catheter, the various types of mask and the tent have, in recent years, become familiar as friendly instruments of treatment and are no longer regarded as gloomy announcers of the embalmer's visit. It is now rarely necessary to convince the patient and his family of the need for oxygen therapy; more often they expect and request it.

For prolonged therapy, the modern tent is the most comfortable and effective way of administering oxygen. The transparent canopy, the quiet operation and the ability to dispense with ice for cooling represent relatively recent improvements. The optimal concentration required must be gauged according to the estimated need of the individual patient. To relieve hypoxia in the ordinary case of cardiac infarction a concentration of 45 to 50 per cent suffices. With careful attention to the prevention of leaks, this can be obtained with a flow of 12 to 13 liters per minute. Somewhat higher concentrations (60 to

65 per cent) can be reached with an oxygen inflow of 15 to 18 liters per minute. Fluctuations to lower levels at intervals during the course of a day are unavoidable because of the necessity of opening the tent periodically for nursing care and feeding.

The mask is useful particularly when a tent is not quickly available or when relatively high concentrations are wanted. Pure oxygen will sometimes relieve severe pain when a mixture fails; but it should not be given for more than 6 hours at a time because, if inhaled for longer periods, it often produces pulmonary irritation and has been known to cause edema of the lungs.[3] Its use may be resumed, if indicated, after the lapse of several hours. A concentration of 70 per cent can be maintained for an indefinite time without toxic effects.

Administration by nasal catheter is the least effective technique, though the simplest. A humidifier in the circuit is used to prevent drying of the throat. The flow should usually be regulated at 5 or 6 liters per minute, which yields a concentration in the inspired air of about 36 to 38 per cent. At 8 liters, 42 per cent can be attained. When greater concentrations are desired the position of the rubber tube may be tried in the oropharyngeal position. However, this placement is apt to cause irritation and, as a rule, is not well tolerated for long periods. The catheter requires lubrication at frequent intervals and cleansing at least every 12 hours.

Results

That the pain associated with acute occlusion of a coronary artery might be relieved by oxygen was first pointed out by Rizer[4] in 1929. In the following year, Levy and Barach[5] reported a small series of cases in which oxygen therapy appeared to influence the course of the illness in a favorable manner and concluded that in some instances it might be responsible for the saving of life. Other workers[6] soon confirmed these observations and in 1934 the same authors[7] published a second paper in which they amplified their earlier findings on the basis of further experience. The use of oxygen in the treatment of suitable cases of cardiac infarction has become accepted practice.

It is difficult to estimate the effects of this procedure on mortality or on the incidence of complications in view of the diverse clinical picture and because, in order to obtain a series of control observations, it would be necessary to withhold oxygen when the need for it might

be urgent. What at first were impressions have been fortified, however, by the repeated experience of many workers in all parts of the world, so that specific inferences are justified.

1. Oxygen therapy brings about subjective improvement. Pain is lessened or abolished, the heart rate falls, and respiration is slower and less labored. The patient is no longer restless. It is possible to curtail materially or stop entirely the use of opiates and sedatives.

2. The state of shock gradually disappears.

3. Cyanosis is diminished or abolished.

4. The onset of congestive failure may be prevented and oxygen aids in controlling it, after its occurrence.

5. The temperature, when elevated, tends to fall.

6. Cheyne-Stokes breathing, if present, is gradually followed by regular respiration.

7. Of great significance is the fact that interruption of oxygen therapy before adequate readjustment of circulatory conditions has taken place results in recurrence of the symptoms and signs just described. Resumption again proves helpful.

Not all of these beneficial effects are to be anticipated in every case; but not infrequently an apparently hopeless situation shows a sharp turn for the better and improvement can be dated from the first day on which oxygen was given. The occurrence of sudden death while a patient is in an oxygen tent is uncommon, perhaps because ventricular fibrillation is less likely to occur when myocardial hypoxia is reduced. Oxygen therapy does not appear to prevent extension or recurrence of the thrombotic process or lessen the likelihood of emboli; reliance is now placed on the use of anticoagulants for these purposes. But it does lighten the burden thrown on a myocardium that has received a sudden, damaging shock. Thus, during the period of greatest stress, it affords an added margin of safety which may be sufficient to promote recovery.

The length of time that oxygen administration should be continued, as in the case of indications for its use, defies precise definition. It will vary in each patient. A fair average might be given as one week; but much longer residence in a tent is often necessary and may lead to recovery. As improvement occurs, the periods out of oxygen for meals, for bathing and for defecation will give a clue as to how well the circulation is able to carry on in room air. Sudden and sustained increase

in pulse or respiration, the occurrence of cyanosis or the appearance of dyspnea or anginal pain indicate that oxygen is still necessary. Sometimes, premature removal will be followed by the gradual onset of congestive failure, as shown by shortness of breath, diminished output of urine, appearance of edema and the presence of rales at the bases of the lungs. Return to the tent is then necessary. On the other hand, if, after slowly increasing the length of time out of oxygen, none of these signs is noted, the patient may be kept in room air for progressively increasing periods during the day, with return to the tent at night. In the course of several days inhalational therapy is entirely discontinued.

Nothing has been said during this discussion, of other aspects of treatment for the patient with cardiac infarction. It should not be inferred from this omission that oxygen is the only form of aid or indeed, the one which is necessarily the most important. Rest, opiates and sedatives, digitalis or quinidine when needed, the mercurial diuretics, the anticoagulants, dietary regulation and good nursing care all have their place in the regimen. It is the proper admixture which makes for a successful outcome.

Summary

Anoxemia of a portion of the heart muscle and hypoxia of all organs and tissues of the body occur in varying degrees after acute coronary occlusion and cardiac infarction. Oxygen lack is manifested by a group of characteristic symptoms and signs of disordered function. Administration of oxygen by inhalation relieves distress and helps in restoring circulatory balance. In certain instances, its effective use is the crucial factor in saving life.

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ANOXIC EFFECTS ON THE ELECTROCARDIOGRAM PRODUCED BY THE 2-STEP TEST

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PAIN in the chest is a common symptom in many extracardiac diseases and in functional conditions. Usually the pain from such sources as spondylitis, gallbladder disease, hiatus hernia, colitis, peptic ulcer, pneumonia, and pneumothorax can readily be differentiated from angina due to coronary artery disease, and from such diseases as anemia or hyperthyroidism. Occasionally it simulates anginal pain, or the latter may be atypical. In these cases the differential diagnosis is often difficult, since patients with coronary artery disease and angina frequently (37 per cent of 600 patients seen in consultation) appear to be normal upon examination, including a 12-lead resting electrocardiogram. Keefer and Resnik were the first to attribute angina pectoris due to coronary disease to anoxia of the myocardium, and this explanation is generally accepted. They and other authors pointed out the occurrence of RS-T depression in the electrocardiogram during spontaneous attacks of angina and in generalized anoxia. Levy, Bruenn and Barach used quantitative tests based on these changes in the electrocardiogram induced by inhaling 10 per cent oxygen to detect coronary insufficiency. Exercise produces similar alterations in the electrocardiogram in patients with coronary disease, and the "2-step" exercise electrocardiogram was introduced to standardize the effort. The similarity of changes seen in the electrocardiogram in spontaneous angina, during the "2-step" exercise test and, in the anoxemia test, indicates that myocardial anoxia or ischemia is

the cause of these changes. When the 2-step exercise produces alterations in the electrocardiograms, coronary insufficiency and myocardial ischemia are present. We believe that the RS-T depression below the baseline seen in a positive "2-step" or anoxemia test indicates ischemia of the subendocardial region of the myocardium, which is the area most sensitive to anoxia. Alterations in this area produce RS-T depression, whereas subpericardial injury produces elevation.

It must be emphasized that the coronary insufficiency produced by exercise is not necessarily associated with organic heart disease but may appear in functional states. In coronary artery disease the exercise increases the work, and the amount of blood which can flow through the diseased arteries is insufficient to meet this augmented demand. In functional coronary insufficiency, without coronary disease, increased "sympathetic" tone and "spasm" of the coronary arteries, resulting in a diminished flow through the normal vessels, have been postulated.

It is not generally known that in persons of tense, nervous makeup or under emotional stress abnormal changes in the electrocardiogram may occur at rest, as well as following exercise or during anoxemia. Frequently these changes are attributed to coronary disease and the patient is treated accordingly. Biörck and Pannier and Biörck were aware of this and employed ergotamine to distinguish between organic and functional coronary insufficiency. Recent experiments by Pordy, Arai and myself, with dihydroergocornine (DHO-180) suggest that this drug may be used for this purpose with greater success.

In a comparison of the exercise and anoxemia tests, the former has been shown to be definitely the more sensitive. We have found that the anoxemia test gave positive results in from 20 to 30 per cent of patients with definite coronary artery disease; other authors have reported up to 50 per cent positive. On the other hand, the double "2-step" is positive in practically every case of organic disease; if the result of the test is negative, coronary insufficiency is practically excluded. One physician has made the point that the single "2-step" electrocardiogram may show normal conditions and the anoxemia test result be positive. It must be obvious that comparison must be made with the double "2-step" test and we have repeatedly emphasized this. The latter gives positive results in approximately one-third more cases than the single test. If the single "2-step" test shows a negative result, the double "2-step" test should be performed. We have frequently observed a positive double "2-step"

electrocardiagram in a patient with a negative anoxemia test but not the reverse.

In functional coronary insufficiency, the anoxemia and "2-step" test results may both be positive; actually the anoxemia test may be the more strongly positive since the tense patient is apt to be more apprehensive during inhalation of 10 per cent oxygen.

The occurrence of a negative finding after the anoxemia test in from 50 to 70 per cent of patients with coronary disease has been attributed to the variation in the oxygen saturation of the blood that occurs during the test.

In both the "2-step" and anoxemia tests the precordial lead has proved the most valuable.

The "2-step" exercise electrocardiogram is of greatest value when there is no objective evidence of heart disease. It is also useful in differentiating various gastrointestinal, pulmonary and somatic lesions from coronary disease. It is of benefit in annual examinations of persons over the age of 35 and those engaged in strenuous activities, e.g., athletes, policemen and firemen, military personnel. It is now used by civilian aviation companies to determine the reaction of pilots to high altitude. Some of the sudden deaths that have occurred among pilots and athletes might have been prevented if an exercise test had formed part of the physical examination. The "2-step" test should not be performed on a patient who has a definite anginal syndrome and in whom a resting control electrocardiogram shows an abnormality or on one who shows other objective evidence of heart disease. In thousands of "2-step" tests we have never experienced untoward results but we have always observed precautions. The double "2-step" was given only after a negative single "2-step" and the test was stopped when pain or other symptoms appeared.

*INHALATIONAL AND AEROSOL THERAPY IN PNEUMONIA, PULMONARY EDEMA AND BRONCHIECTASIS**

INHALATIONAL AND AEROSOL THERAPY IN PNEUMONIA

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Inhalational Therapy

Pneumonia as discussed here includes all the acute pneumonias irrespective of etiology. The term most often refers to pneumococcus pneumonia by reason of its predominant frequency, but the statements made are applicable to pneumonia due to the streptococcus, staphylococcus, Friedländer's bacillus, Hemophilus influenzae, and the tubercle bacillus as well as to primary atypical pneumonia.

The treatment of the pneumonias has been profoundly changed during the past ten years by the sulfonamides and more recently by the antibiotics. Of the latter, penicillin has been most responsible for this change. As is well recognized, the use of penicillin in pneumococcus pneumonia has brought about a sharp drop in the mortality rate, a definite shortening of the febrile period, a decreased frequency of multiple lobe involvement and a greatly decreased incidence of complications. Not only are organic complications dependent upon bacterial infection rarely seen, but there has also been a sharp reduction of those physiological effects of pneumonia which were so frequently present in severe cases, namely cyanosis, tachycardia and ectopic rhythms, disorientation and delirium.

In a comparable manner, the antibiotics have had striking effects in streptococcus and staphylococcus pneumonias, and have been effective in some cases of Friedländer's bacillus pneumonia. Aureomycin has

* Given December 9, 1949 at The New York Academy of Medicine.

been effective in primary atypical pneumonia, and streptomycin has been shown to induce resolution in the exudative lesions of tuberculosis.

Before the advent of chemical and antibiotic therapy it was well recognized that bacteriemia and anoxia were predominantly responsible for the high death rate. Bacteriemia was a serious hazard and gravely increased the mortality rate. Similarly, reduced oxygen saturation of the arterial blood was found in all but the mildest cases, and was associated with a serious clinical course and high mortality. The degree of anoxia paralleled the death rate; pneumonia patients with arterial saturation of only 60 or 70 per cent rarely recovered. Those who did not see pneumonia patients before the sulfonamide-antibiotic period of treatment can have little idea of the critical features of this illness so dominated by infection and anoxia.

In the average treated case of pneumonia today there is no need for oxygen therapy. If the diagnosis is made early and antibiotic therapy is effective, the illness is over before anoxemia can become a serious hazard. The death rate, however, is not yet zero. There may be a definite need for administration of oxygen when antibiotic therapy has been delayed or in those patients that fail to respond to antibiotics within a few days. It may be of great help in older patients or in those with serious underlying disease such as nephritis, myocardial infarction or disease of the brain. Postoperative patients with pneumonia or patients with aspiration pneumonia may be helped by oxygen. Patients with Friedländer's bacillus pneumonia, influenzal pneumonia or widespread primary atypical pneumonia may be carried safely over the danger point until recovery occurs spontaneously or until antibiotics are effective. It is in this category of cases that anoxia is likely to be a factor in recovery and it is here that oxygen is an indispensable supporting agent.

The anoxemia of pneumonia is of the anoxic type; that is, it is due to failure to saturate arterial blood in pulmonary capillaries. It is produced by several mechanisms. Early in the disease, the persistence of pulmonary circulation through partially consolidated, congested lung, results in the return of unoxygenated blood to the left auricle. Shallow respiration, so common in pneumonia, and frequently due to pleural pain, may cause anoxemia by producing a relative increase in dead space. Pulmonary edema in unconsolidated portions of the lungs prevents the diffusion of oxygen through alveolar walls. A combination

of these factors may operate at the same time and cause oxygen want of clinical importance.

The symptoms of anoxemia may be overlooked entirely or they may be attributed to infection or other causes. For instance, delirium was commonly attributed to "toxemia," the role of anoxia being entirely overlooked. The effects on one system may overshadow those on another. Cyanosis is an unreliable sign, frequently overlooked, and it may be entirely absent if the patient has severe anemia. Tachypnea and tachycardia are common effects of anoxia. Premature systoles, auricular fibrillation and flutter may appear, especially in the older age groups. The gastrointestinal system may show the effects of anoxemia by nausea, vomiting and jaundice. Abdominal distention is common, and it in turn may produce shallow breathing, further increasing anoxemia. Cerebral symptoms are frequently overlooked, especially restlessness, memory defects and insomnia. Disorientation as to time and place, and delirium are frequent with severe reduction of arterial blood saturation. It is generally admitted that anoxemia has not frequently enough been given its full responsibility in causing severe symptoms and death.

The aim in treatment is to prevent the occurrence of anoxemia whenever this is feasible or, if evidence of oxygen lack has already appeared, to relieve this lack as soon as possible by adequate oxygen therapy. Anoxemia may be expected in pneumonia patients who fail to respond to antibiotics within two days and in those who have persistently shallow, painful respirations. This is especially true of older persons. These patients should receive oxygen therapy even before the need is plain. Treatment should be started at the earliest possible moment in those patients with signs or symptoms of anoxemia such as tachycardia, rapid respiratory rate, cyanosis, abdominal distention or restlessness or disorientation. It is wrong to wait for spontaneous improvement; anoxemia is a dangerous physiological state to gamble with. Procrastination is often based on the belief that changes produced in anoxia are reversible. This is not always so. Brain damage may be permanent.

The beneficial effects of the inhalation of high concentrations of oxygen in pneumonia patients have been observed in three ways: First, the arterial blood oxygen has been raised materially, often to normal levels. Second, mortality has been lower in series of oxygen-treated

cases than in untreated groups. Third, improvement has been seen clinically in the following ways: the patient is more comfortable and sleeps more restfully; respirations are easier and slower; the pulse rate is slower and abnormal rhythms may be abolished; cyanosis is less or may disappear; the temperature often falls one or two degrees. Delirium and disorientation may disappear and abdominal distention be lessened.

Oxygen may be administered by nasal catheter, mask, chamber or tent. Each of these techniques has certain advantages and disadvantages which may be stated briefly as follows: The nasal catheter is the least expensive method but it is also the least satisfactory. It is usually irritating to the nose and pharynx, and limits the movement of the head. It may deliver an oxygen concentration between 35 and 50 per cent depending on the oxygen flow and the placement of the catheter, but it is *not reliable*. It often falls out during sleep and is usually torn out by the irrational patient. Generally speaking, the catheter method is unreliable. The face mask can deliver a higher concentration of oxygen than the catheter, and it is less expensive than a tent. However, a mask is of no value unless it is applied closely to the face, and most patients cannot tolerate it for more than a few hours. Sensitive, irritable patients will attempt to push it off the face. The oxygen chamber or room is the ideal method of administration, but it is available to few patients. Not more than two or three hospitals in this city are equipped with such rooms.

For all practical purposes, a good oxygen tent equipped with a quiet motor and a transparent canopy is the best all around method of administration. It is comfortable, does not cause the patient to feel enclosed or crowded, and can be used continuously to keep the patient in an oxygen-enriched atmosphere. A tent should have an atmospheric oxygen concentration between 50 and 60 per cent, the temperature should be about 68 degrees and the humidity should be low. It is a common error to open tents unnecessarily and so deprive the patient of sorely needed oxygen. Once placed in a tent, the patient should remain in the high oxygen concentration until he has no further need of such therapy. It is a mistake to use the tent intermittently. Generally speaking, if a patient is uncomfortable in a tent there is something wrong with the tent or with the technique used. The oxygen concentration should be determined at frequent intervals. After the patient's temperature has dropped to normal, it is better to continue the use of the tent for an additional

twenty-four hours. After this, the concentration of atmospheric oxygen should be reduced gradually before the patient is removed from the tent. An oxygen flow of 12 liters per minute will usually deliver an atmospheric content of 50 to 60 per cent, provided the tent is kept closed. Soda lime is unnecessary in the circuit because with an oxygen flow of 12 liters, or more, per minute diffusion from the tent is sufficient to keep the CO_2 from rising to uncomfortable levels.

Aerosol Therapy

Aerosols for the direct therapy of bronchial and pulmonary diseases have been used for about fifteen years. Epinephrin mist for the relief of bronchial spasms in asthma was the first popular application of this method. This was followed by aerosol sulfonamides, which were said to have the advantage of producing high bronchial levels and low blood levels. Later, other therapeutic aerosols with oxygen flows were introduced for topical therapy of the respiratory tract and for rapid systemic effects through absorption from the inner surface area of the lungs. These have been used in a variety of diseases of the lungs and bronchi.

This discussion is limited to the aerosol therapy of pneumonia. Considerable knowledge of the clinical application of penicillin aerosol has been gained from the work of Barach and his group, Segal and his colleagues, Humphreys and Joules, Vermilye, and Southwell. It has been shown repeatedly that penicillin aerosol penetrated the lungs rapidly, diffused into the blood stream and was excreted into the urine. The pharmacodynamics of pulmonary absorption in man has recently been discussed by Gaensler, Beakay and Segal. It is recognized that blood levels well above the minimum bacteriostatic requirements to inhibit the growth of non-resistant staphylococci and streptococci can easily be obtained. Effective blood levels ranging from 0.028 to 0.055 units per cc. have been reported by Segal and his group in cases of bacterial pneumonia. Small groups of patients with bacterial pneumonia have been treated by various investigators with penicillin aerosol with good results. Wilson has demonstrated the effectiveness of aerosol penicillin in experimental type 1 pneumonia in rats.

A review of the literature of penicillin aerosol in the treatment of pneumonia can leave no doubt of its effectiveness. However, since the parenteral route of administration of penicillin is simple, reliable and effective, it remains the method of choice in the treatment of pneumo-

coccus pneumonias. There are other considerations which weigh heavily in favor of parenterally administered penicillin. There is no proof that aerosol penicillin acts in pneumonia except after absorption. Two patients treated with aerosol penicillin are cited by Segal in which recovery from pneumonia occurred even though no penicillin was detectable in the blood stream. This could very well represent spontaneous recovery from the disease. Secondly, since bacteriemia is a serious hazard in pneumonia, the route of administration which is most certain to yield effective blood levels at the earliest possible moment is the method of choice. By the same token, combined aerosol and parenteral administration should be no more effective than the parenteral route alone. No indisputable clinical evidence has been put forward to prove the contrary.

This leaves the problem of aerosol therapy in bacterial pneumonias due to organisms other than the pneumococcus—namely the streptococcus, staphylococcus and Friedländer's bacillus. Segal and his colleagues state that "for the management of streptococcus and staphylococcus pneumonia and pneumonia due to penicillin-susceptible strains of Friedländer's bacillus, we are of the opinion that penicillin aerosol is more effective than parenteral therapy alone." They do not cite the evidence on which their conclusion is based. This statement would be more easily acceptable if it were based on a sufficiently large series of cases. Furthermore, the choice need not be between parenterally administered penicillin which had already failed to effect a cure and aerosol penicillin therapy. With the availability of other antibiotics such as aureomycin and streptomycin, it would seem more desirable to attempt treatment with one or more of these.

In conclusion, it would appear that for the treatment of pneumococcus pneumonia, parenterally administered penicillin remains the method of choice. In cases of pneumonia due to the streptococcus, staphylococcus and Friedländer's bacillus, the value of aerosol penicillin over parenterally administered penicillin is unproved. The use of other available antibiotics is suggested.

PRESSURE BREATHING WITH OXYGEN AND HELIUM OXYGEN IN PULMONARY EDEMA AND OBSTRUCTIVE DYSPNEA*

HYLAN ARTHUR BICKERMAN and GUSTAV JULIUS BECK

THE treatment of pulmonary edema has always presented a serious challenge to the attending physician. The increasing incidence of this disease is due in part to an aging population in which heart disease is prevalent and to the increasing use of toxic gases in industry and war. However, this clinical entity is frequent during the course of other serious illnesses, such as atypical and virus pneumonia, shock, and bulbar poliomyelitis.

The use of inhalation of gases under positive pressure for the treatment of obstructive dyspnea and acute pulmonary edema was developed independently by Poulton[1] in England and Barach[2] in this country in 1936. Historically, it is of interest that Oertel[3] in 1878 used compressed air in the treatment of a patient with severe asthma. In 1896, Norton[4] reported a case of pulmonary edema due to carbolic acid poisoning which responded rapidly to the application of forced respiration under positive pressure. Several years later, Haven Emerson[5] and, subsequently, others showed that edema of the lungs produced in rabbits by intravenous adrenalin could be relieved by artificial respiration. Barringer[6] made use of this suggestion in the successful treatment of a patient with cardiac insufficiency who developed acute pulmonary edema.

While inspiratory positive pressure respiration was commonly accepted as a method of resuscitation in accidental asphyxia, continuous pressure breathing was first used clinically, in the treatment of edema and obstructive dyspnea.[7] Later, high altitude flying stimulated intensive studies on the physiologic effects of various forms of pressure breathing.[8] Newer techniques, including cardiac catheterization, have given additional and more exact information on the circulatory and respiratory effects in man.[9]

Pulmonary edema presents a characteristic clinical picture manifested

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by bubbling rales in the lungs and severe anoxia. The physiologic factors involved in the transudation of serous fluid from pulmonary capillaries into the alveoli depend upon the resultant of forces represented by the hydrostatic pressure within the capillaries, the colloid osmotic pressure, capillary permeability and lymphatic drainage.

Welch[10] in 1878 postulated that a relative insufficiency of the left ventricle resulted in an accumulation of blood in the lesser circulation resulting in severe congestion. In addition to the increased hydrostatic pressure, local areas of anoxia would effect a change in capillary permeability. An increase in capillary permeability may be induced by specific irritants, local inflammation, toxemia and severe anoxia. This factor is important in the pathogenesis of pulmonary edema occurring in the course of pneumonia, peripheral circulatory failure, and gas poisoning.

Other factors which may play a role in edema of the lungs are:

Severe depression of the colloidal osmotic pressure of the blood in certain disease states such as nephrosis and hepatic insufficiency.

Neurogenic and reflex mechanisms occurring as a result of cerebrovascular accidents, trauma to the skull and disease of the central nervous system.[11]

In obstructive dyspnea due to severe asthma or to lesions of the tracheobronchial tree, the lung capillaries are exposed to a high negative intrapulmonary pressure on inspiration which exerts a suction-like action on the capillary walls and tends to further pulmonary congestion.

As a result of the investigations of Barach and his collaborators,[7] it was observed that the use of positive pressure breathing decreased the effort necessary for inspiration with a corresponding decrease in the pathologically elevated negative pressure. In addition, continuous pressure breathing had the following physiologic advantages in the treatment of pulmonary edema and obstructive dyspnea:

Exerted a direct opposing pressure on the external surface of the pulmonary capillaries and counteracted in some measure the elevated hydrostatic pressure.

Served to retard the entrance of blood into the right side of the heart, thereby diminishing the accumulation of blood in the lungs.

Provided greater patency of the tracheobronchial airway, especially during the expiratory cycle.[12]

Pressure Breathing Equipment

There are two general types of pressure breathing, 1) intermittent and 2) continuous. In the former, the major part of pressure is applied during expiration (expiratory pressure breathing) or during inspiration (inspiratory pressure breathing).

1.(a) *Expiratory positive pressure* may be applied with relatively simple devices requiring the patient to exhale against a resistance and thereby increase the intrapulmonary pressure during expiration. Inspiration takes place at the customary negative pressure. The Meter mask[13] is equipped with a metal disc in front of the expiratory flutter valve, in which expiration takes place through a restricted orifice, the size of which regulates the pressure. Greater accuracy in the control of pressure is obtained when expiration is conducted through a water bottle calibrated in centimeters.[14,15]

The use of positive pressure during expiration is useful in the treatment of acute pulmonary edema as a result of alterations in permeability of the pulmonary capillaries, and left ventricular failure. It is customary to begin treatment with an expiratory pressure of 5 cm. of H_2O, which is gradually lowered to atmospheric pressure when improvement is manifested. An oxygen concentration of from 40 to 60 per cent is employed. Expiratory positive pressure is also used to prevent or control the oozing that takes place from the tracheobronchial tree following tracheotomy. When this is used, the tracheotomy tube is prolonged so that expiration proceeds through a valve into a water bottle set at a pressure of 4 to 5 cm. of H_2O, and this is gradually lowered during a period of twelve hours to 1 cm. of H_2O.[16]

Expiratory pressure breathing results in rather labored expiration and, since there is no aid to inspiration, the breathing effort is greater than with inspiratory or continuous pressure.

(b) *Inspiratory Positive Pressure Breathing.* Gas enters the lungs under positive pressure in inspiration; pressure is then automatically released and expiration occurs as a passive act. Such apparatus is useful in the treatment of patients with depressed or failing respiration as in coma or poisoning. The respirators give adequate pulmonary ventilation when spontaneous respirations have ceased. The essential features of these appliances are a high pressure oxygen tank, a demand valve and a second or "cycling" valve.[17] It should be emphasized that these devices

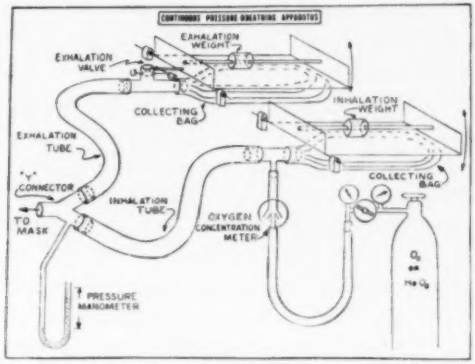

Fig. 1—A double bellows type apparatus which provides continuous positive pressure with either oxygen or helium-oxygen mixtures over the range of 0 to 14 cm. water pressure.

will cycle also with the patient's own respiration following recovery of spontaneous breathing as opposed to the Drinker type respirator.

Since inspiratory positive pressure breathing, conventionally called "intermittent," provides a mean positive pressure during the entire respiratory cycle, it is also effective in the treatment of acute pulmonary edema. A serious defect in its use on a dyspneic patient is the inability of the current models (Pneumolator and Emerson) to provide a rapid immediate volume of inflow. Motley[18] has reported that in some instances the inspiratory velocity of the dyspneic patient will exceed the capacity of the apparatus. The patient inhales against a resistance with a sensation of increased dyspnea or suffocation. This would be especially true for a patient with obstructive dyspnea. In addition, a significant degree of hyperventilation may occur on intermittent positive pressure breathing. A research model with a high inflow capacity (100 L/min.) has been devised but it is not commercially available at present.

2. *Continuous Pressure Breathing.* Pressure is employed in both phases of respiration. The degree of comfort in breathing is much greater than with expiratory pressure breathing alone, and that is especially true when the variation between expiratory and inspiratory pressure is kept at a minimum.

An effective apparatus for the administration of oxygen and helium-

oxygen mixtures is the positive pressure hood.[19] This is useful in the treatment of severe asthma and obstructive dyspnea produced by lesions in the tracheobronchial passageway. Since this is a closed circuit apparatus, it is important to provide efficient cooling and absorption of carbon dioxide with soda lime. Pressures are maintained by a motor blower unit and a pressure control water valve.

A relatively simple bellows device for employing continuous positive pressure has been developed* (Fig. 1). Inspiratory pressure is rapidly built up when oxygen at 15 L/min. is passed through a specially constructed injector meter which delivers 65 liters of gas per minute at an oxygen concentration of 38 per cent to a weighted bag of 2 liters capacity. The expired gases pass into a similarly weighted bag which is equipped with a butterfly type valve. The degree of expiratory and inspiratory pressure is easily adjusted by means of sliding weights. An airtight seal over the face is accomplished by a light plastic Bennett mask with an inflated cuff. With lower rates of inflow, the building up of inspiratory positive pressure is less rapid. When helium-oxygen mixtures are employed, the injector meter is not used. The apparatus is equipped with an emergency inspiratory valve which permits ingress of air if the inspiratory collecting bag should for any reason collapse. The patient is thus protected against breathing under negative pressure. In general, it must be said that inspiratory pressure breathing appeared to us to be somewhat more comfortable than either continuous or expiratory pressure breathing.

The physiologic effects on respiration and hemodynamics of continuous pressure breathing employing the bellows apparatus was studied in eighteen normal subjects at mean mask pressures of 6 to 12 cm. of H_2O. To obtain measurements of the relative cardiac output and stroke volume, we employed a modification of the photo-electric method of ballistocardiography as developed by Dock[20] in which motion of the body is transmitted to a rigid metal bar placed across the shins which is in contact with an occulting plate mounted on frictionless jewelled points. The shadow cast by the occulting edge on a photocell results in changes in electric potential which is recorded by a direct writing electrocardiograph. These records are standard and reproducible with a time lag of less than 0.005 seconds (Figs. 2 and 3).

While the ballistocardiograph, as developed by Starr and others, was

* The bellows type continuous positive pressure apparatus can be obtained from the Oxygen Equipment Manufacturing Co., Norwalk, Conn.

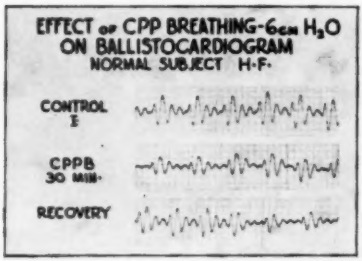

Fig. 2

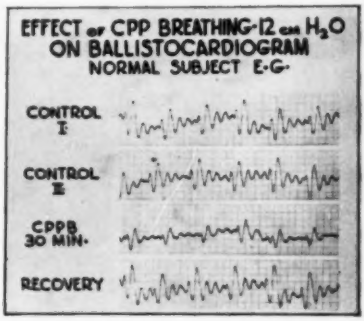

Fig. 3

Figs. 2 and 3—Ballistocardiograph tracings obtained by the Dock method employing a photo-cell pickup.

originally employed to estimate the volume of ventricular ejection, the assumptions made in deriving the formula are numerous, and the reliability of absolute values for stroke volume may be seriously questioned, since the amplitude of the waves depends on ejection velocity rather than volume alone. Since we were interested in relative stroke volumes rather than absolute values, a simplification of Starr's original formula was employed discarding factors K and A.[21]

$$Sv = K\sqrt{(3I + 2J)\,AC^{3/2}}$$

$$\text{Rel } Sv = \sqrt{(I + J)\,C^{3/2}}$$

As Fenn[22] has pointed out, since the ballistocardiograph is sensitive enough to demonstrate the normal respiratory variation in cardiac output, it was felt that any significant changes caused by pressure breathing would be apparent on the tracing and that relative values obtained on the same subject under controlled experimental conditions should be fairly reliable.

In general, there was a slight but variable increase in respiratory rate, pulmonary ventilation and tidal air. In ten subjects at a positive pressure of 6 cm. of H_2O the average increase in pulmonary ventilation was 6 per cent. At 12 centimeters positive pressure, the average increase was 9.5 per cent. These changes were statistically not significant. The relative stroke volumes and cardiac outputs computed from ballistocardiographic tracings showed a significant fall averaging

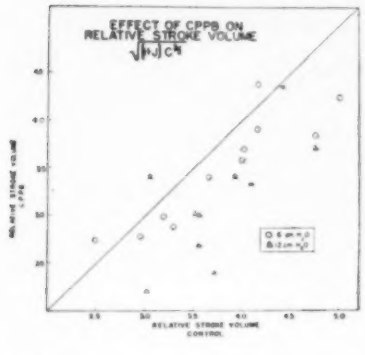

Fig. 4—Graphic illustration of the change in relative stroke volumes; values obtained during a control period at ambient pressure are compared with data on the same subject during a positive pressure period.

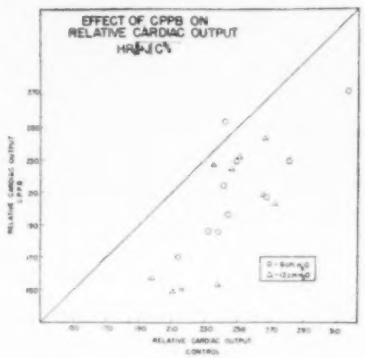

Fig. 5—The relative cardiac outputs while breathing 40% oxygen at atmospheric pressure are compared to continuous positive pressure breathing at 6 and 12 cm. of water pressure.

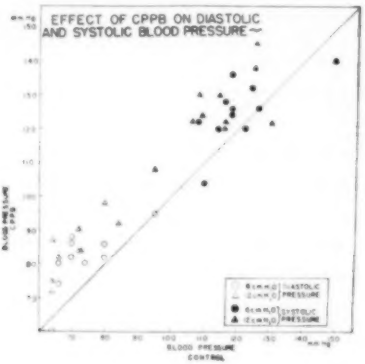

Fig. 6—This comparison graph illustrates the rise in both systolic and diastolic blood pressure accompanying the application of continuous positive pressure.

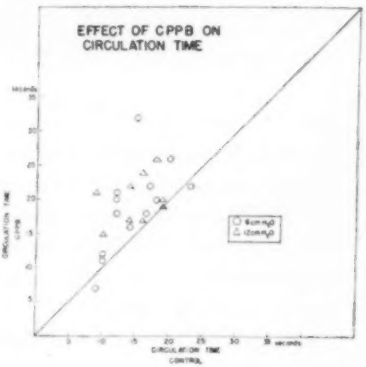

Fig. 7—Circulation time studies with Decholin have been plotted to illustrate the change accompanying continuous positive pressure breathing.

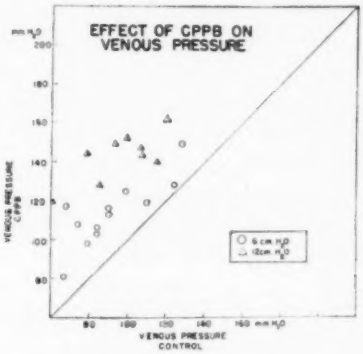

Fig. 8—The striking relationship between the height of the applied pressure and the increase in venous pressure is demonstrated.

6 and 14.6 per cent respectively at 6 cm., and 18 and 20.5 per cent at 12 cm., the magnitude of this decrease being related to the height of the mean mask pressure (Figs. 4 and 5). Minor variations in the heart rate occurred. There was a distinct rise in both systolic and diastolic blood pressure. The elevation in diastolic pressure was greater than in the systolic, resulting in a slight decrease in pulse pressure (Fig. 6). The circulation time for decholin was prolonged (Fig. 7), and the increase in venous pressure was highly significant, with the average elevation being directly proportional to the mean mask pressure (Fig. 8). The hematocrit and plasma protein studies showed no appreciable change from the control level (Table I).

Discussion

These results are on the whole in agreement with previous studies by Barach, Eckman et al,[23] employing continuous pressure breathing in normal, cardiac, and asthmatic patients. Similar results were obtained by Motley and Cournand[24] and Otis and Fenn[22] working with intermittent pressure breathing in the same mean pressure range.

While all observers have reported a consistent fall in the cardiac output of normal subjects with pressure breathing, Cournand remarked on certain differences in the behavior of cardiac patients. In 3 of 9 cardiac patients on a mean mask pressure of 5 to 7 mm. of mercury, the

TABLE I—INFLUENCE OF CPPB UPON HEMODYNAMICS IN NORMAL SUBJECTS

Subject	Mean Mask Pressure cm H_2O	Per Cent Change From Ambient									
		Heart Rate	Stroke Volume	Cardiac Output	Blood Pressure			Venous Pressure	Circulation Time	Hematocrit	Total Proteins
					Systolic	Diastolic	Pulse				
W.M.	6	0.0	— 8.0	— 8.0	— 1.6	+ 8.7	—16.7	+27.8	+113.3	0	+4
D.W.	6	— 3.6	—19.5	—22.5	+11.4	+22.9	— 8.7	+26.2	+29.4	0	+3
G.M.	6	+12.2	— 6.1	+ 4.5	+ 6.8	+ 2.5	+15.8	+ 8.2	—22.2	0	
E.G.	6	— 4.5	— 4.1	—11.2	+ 5.1	+22.9	—20.8	+ 0.8	+75.0	0	—3
M.L.	6	—17.3	— 6.0	—21.8	+ 6.4	+25.7	—18.5	+21.0	— 4.3	0	+7
L.E.	6	—18.4	+ 5.3	—13.9	+ 5.3	+17.1	—13.6	+16.4	+11.1	+4.4	+7
H.F.	6	— 3.6	—15.5	—18.5	+13.0	+12.1	+14.3	+20.9	+30.0	0	—7
M.C.	6	—10.3	—13.0	—19.8	— 5.5	— 4.2	— 4.3	+22.9	+28.0	—2.3	—7
S.B.	6	— 8.1	— 9.4	—19.7	+15.3	+17.5	+ 7.7	+64.3	+14.3	0	+7
I.P.	6	—16.3	+10.0	—20.6	— 2.8	0.0	— 8.2	+45.9	+ 2.9		
J.J.	6	— 3.1	— 5.8	— 8.6	0.0	+ 9.4	—13.1	+22.8	+50.0	—4.7	+5
R.B.	6				+ 3.7	+ 8.1	0.0	+17.9	+67.9	0	
R.C.	6				+ 9.6	+18.2	— 5.3	+47.0		0	
H.S.	6				— 3.3	+15.6	—24.1	+38.9	+20.0		
Average		— 6.6	— 6.0	—14.6	+ 4.5	+12.6	— 6.8	+27.2	+31.9	—0.3	+0.45
I.F.	12	— 2.9	—27.2	—29.4	— 6.2	+ 9.5	—34.8	+33.7	+57.2	0	0
E.G.	12	+ 0.0	—21.8	—21.5	+ 5.2	+16.7	—13.6	+34.2	+133.3	0	—6
M.L.	12	— 8.9	—32.9	—25.4	+13.8	+33.9	—15.9	+50.6	+ 5.3	+4.3	—4
E.R.	12	— 7.1	—15.0	—20.7	+15.1	+15.1	+15.2	+112.2	+50.0	+2.3	+3
S.E.	12	— 8.2	—24.3	—30.6	+13.7	+12.5	+16.2	+55.1	+ 6.2	+5.3	+7
F.H.	12	—12.8	+11.8	— 3.4	+ 8.7	+22.5	—14.9	+39.4	0.0	0	0
J.M.	12	+ 6.2	—13.0	— 7.6	+20.4	+25.0	+11.1	+23.5	+21.4	0	0
W.Mc.	12	0.0	—35.3	—35.7	+14.0	+25.0	— 4.8	+60.2	+44.4	+7.0	+9
W.M.	12	+ 2.9	—11.4	— 9.8	+ 3.5	+24.2	—24.0	+84.6	+50.0	0	—9
R.B.	12				+16.0	+17.2	+14.8	+101.7	+20.0	0	—2
R.C.	12				+10.5	0.0	+22.2	+56.9	+77.9		
H.S.	12				+ 3.3	+ 4.2	+ 2.1	+40.8	+11.1		
Average		— 3.4	—18.0	—20.5	+ 9.8	+17.2	— 2.2	+57.7	+39.7	+1.9	—0.8

cardiac output rose an average of 12 per cent. Lars Werko[25] employing the same pressures, obtained a rise in cardiac output of 10 to 35 per cent in two patients in cardiac failure. This may be related to a decrease in filling pressure of the right auricle, permitting the ventricle to empty more completely, and correlates well with McMichael's study of cardiac output in heart failure in which the application of tourniquets to the extremities diminished the venous return and increased the cardiac output, in accordance with Starling's law of the heart.

In reviewing the literature published since 1935, a total of sixty-four case reports were collected in which positive pressure breathing had been employed for pulmonary edema or obstructive dyspnea. Of these, twenty-eight were in pulmonary edema due to acute left ventricular failure; fourteen suffered from status asthmaticus or obstructive dyspnea; thirteen had pulmonary edema secondary to respiratory depression; six were patients with an extensive pneumonic process complicated by pulmonary edema. There was an interesting case of lung edema due to chlorine gas inhalation[26] and two cases reported by Ansbro[27] of pulmonary edema following tracheotomy. In addition, Carlisle[28] reported 316 patients treated with positive pressure who had inhaled toxic fumes. Most of his patients were seen in the so-called "latent" period prior to the onset of frank pulmonary edema.

Most of the patients observed were the worst possible risks and had received without apparent benefit the commonly used medical measures prior to instituting pressure breathing, which was tried as a last resort. Positive pressure respiration should be administered cautiously in shock in which the venous return to the heart is already retarded. The increased intrapulmonary pressure of from 2 to 4 cm. of H_2O may further diminish the flow of blood into the right auricle. When peripheral circulatory failure is suspected, the blood pressure should be followed at 15 minute intervals and positive pressure discontinued if a fall greater than 10 mm. of mercury takes place in the systolic pressure following the application of pressure breathing.

The usefulness of substituting helium for nitrogen in the gas mixture is due to the lower specific gravity of helium.[29] This property makes it possible to breathe through constricted pulmonary airways at almost one-half the effort required for the respiration of air or pure oxygen, thereby lowering the elevated negative pressure within the chest that occurs in obstructive dyspnea.

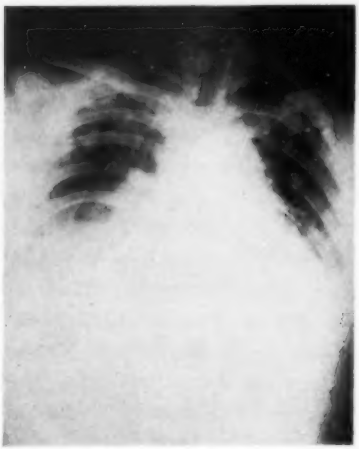

Fig. 9—Portable chest roentgenogram taken on April 26 prior to institution of positive pressure breathing. A major portion of both lung fields is radio-opaque.

Fig. 10—Portable film taken April 30, after 72 hours of continuous pressure breathing at eight cm. water pressure employing a 65 per cent helium 35 per cent oxygen mixture. Considerable clearing has taken place at both bases.

Case Reports

It is apparent that the primary illness in which pulmonary edema occurs as a complication is frequently of such severity that an ultimate recovery cannot always be expected. However, the clearance of lung edema may allow a seemingly moribund patient opportunity to recover from the original disease. Brief case reports of three subjects are presented:

Case 1: J. K., a 44 year old physician, was admitted to the hospital on April 24, 1947 in a semi-conscious state suffering from smoke poisoning after he had attempted to evacuate patients from a burning building. He regained consciousness in an oxygen tent and appeared relatively comfortable for a period of 24 hours. On the 26th of April, he lapsed into semi-coma, became dypneic and cyanotic and temperature spiked to 103°. He was rapidly digitalized, giving aminophyllin and plasma intravenously, and penicillin therapy was instituted. Auscultation revealed the coarse bubbling rales of pulmonary edema. Bronchoscopic examination was a failure because of the marked edema and friability of the tissues. That night he appeared to be moribund. At 8:00 p.m. continuous positive pressure respiration was applied with a mixture of 65% helium, 35% oxygen at a mean mask pressure of 6 cm. of water. The patient's color immediately improved. Respiratory rate fell from 56/min. to 26/min. and within 45 minutes he

regained consciousness with evidence of pulmonary edema having disappeared. He was maintained on positive pressure for 96 hours, since attempts to decrease the pressure resulted in the reappearance of obstructive dyspnea. His clinical course was stormy, being complicated by a pneumonic process of the right, middle and lower lobes with atelectasis of the left lower lobe. He made a complete recovery and was discharged May 13th (Figs. 9 and 10).

Case 2: J. L., a 58 year old man with a 7 year history of hypertensive cardiovascular disease, complained of severe epigastric and chest pain on July 1, 1949. Clinical and laboratory evidence suggested the diagnosis of a dissecting aneurysm of the abdominal aorta. His course was gradually downhill; further episodes of pain suggested extension of the dissecting process. In addition, he had a severe refractory anemia and marked renal insufficiency. On November 7, severe dyspnea and the physical signs of pulmonary edema were elicited. He received digitalis, morphine and mercurial diuretics with no benefit. That evening he was placed on continuous pressure breathing with oxygen at 6 cm. of water pressure. This cleared the coarse bubbling rales within 15 minutes, but rales would recur when the mask was removed. Positive pressure was maintained until the patient's death on the following day.

Case 3: J. B., a 71 year old woman has had hypertension and diabetes for 15 years. Her diabetes was controlled with small daily injections of protamine zinc insulin, while digitalis and aminophyllin served to keep her compensated. While sitting in a chair, she had a sudden episode of severe dyspnea, and examination 30 minutes later revealed the characteristic picture of pulmonary edema. She was immediately placed on expiratory positive pressure breathing with oxygen at 4 cm. of water pressure, and within 45 minutes all evidence of lung edema had cleared. She made an uneventful recovery, and a follow-up two years later showed no further recurrences of pulmonary edema.

Summary

Physiologic studies were carried out on continuous pressure breathing. When compared to inspiratory pressure, employing a type one or type two curve, no differences in cardiac output or in venous pressure were discerned, provided the mean mask pressure of the intermittent type corresponded to the mean of the continuous pressure breathing.

Pressure breathing, employing either continuous or intermittent pressure, is effective in the treatment of acute pulmonary edema. In the control of obstructive dyspnea due to laryngeal obstruction or to asthma, pressure during inspiration, provided either by continuous or inspiratory pressure breathing, was clinically more valuable than expiratory pressure breathing alone.

An apparatus providing continuous pressure breathing is described, in which a mask is employed instead of a hood, the pressure during inspiration and expiration being produced by suitable weights on the oxygen collecting bags. This apparatus has the advantage of providing an adequate flow of oxygen-enriched atmosphere even in the presence of severe dyspnea, in which the present models employing intermittent

inspiratory pressure have been found to yield an insufficient velocity of air flow.

The case histories of three patients with acute pulmonary edema are reported in which the application of continuous pressure breathing was followed by disappearance of lung edema.

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AEROSOL THERAPY IN SINUSITIS, BRONCHIECTASIS AND LUNG ABSCESS

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ANTIBIOTIC aerosol therapy techniques are designed to deposit a nebulin in areas where a close contact can be made with infecting organisms, particularly in regions of the body to which the blood supply does not adequately transport a blood-borne agent to contact bacteria . . . or where there is a selective barrier active to prevent passage of drugs from blood vessels into the area in question. Examples of these areas include the sinuses draining into the nose and the bronchi. Sulfonamide drugs may be found in bronchial secretions in the same concentration as in the blood stream; penicillin, however, does not share this propensity to penetrate into the bronchial lumen. It has been shown that intramuscular injection of penicillin has often failed to alleviate the symptoms of bronchiectasis, whereas subsequent use of antibiotic aerosol has produced good clinical results. The effectiveness of an aerosol depends mainly upon the topical deposition of a quantity of antibiotic sufficient to overcome the pathogenicity of the virulent organisms present.

No attempt will be made in this summary to review the literature on aerosol therapy. The methods and results reported herein have been

taken from studies carried out in Columbia-Presbyterian Clinics over the past six years and from other clinics.*

A number of methods have been developed to produce a nebulin, but even with the variety of methods used, most workers have reported good results from the use of antibiotic aerosols in conditions characterized by infection in the respiratory tract from the paranasal sinuses to the lungs.

The factor of sinusitis in the development of bronchiectasis, especially in children, is not plainly evident; it is difficult to decide which precedes the other, since iodized oil may be visualized in the sinuses following bronchography, indicating that infection may proceed in either direction.

Although penicillin introduced into the nose by a simple nebulizer may counteract naso-pharyngeal infection, the drug is deposited in the sinuses in adequate concentration only if the sinuses are first partially exhausted of their air content by negative pressure followed immediately by nebulization of the aerosol to replace the partial vacuum induced. An apparatus has been designed which allows a negative pressure of as much as 90 mm. Hg to be formed in the sinuses. This consists of two nosepieces and a nebulizer connected to the source of power via a venturi tube. The open end of the venturi is closed to force the gas through the nebulizer into the nose. Then the finger is removed from the open end of the venturi and the patient swallows. While suction in the nose is being experienced, the finger is again placed on the venturi to blow the penicillin aerosol into the now partially evacuated sinuses, and starting the cycle again. The source of air flow required to operate this equipment may be obtained from a standard oxygen or compressed air tank, from a small motor blower pump, from an automobile tire foot pump, or from a hand bulb.

A much more simple apparatus has been recently designed, especially for home use, in which the rubber bulb is the source of both the negative pressure and the nebulizing power. The distal end of the bulb contains no valve (or the valve may be taped over and the ball removed from the proximal valve) so that as the bulb is squeezed a nebulin is produced and as it fills, as it must from the nose, a negative pressure may be produced, provided the other nostril is occluded and the patient swallows. After the nebulizer is charged with penicillin, most conveniently in the form of a

* A more extensive appraisal of advances in the therapeutic use of antibiotic aerosols will appear in a forthcoming paper by A. L. Barach, H. A. Bickerman, B. Garthwaite and G. J. Beck.

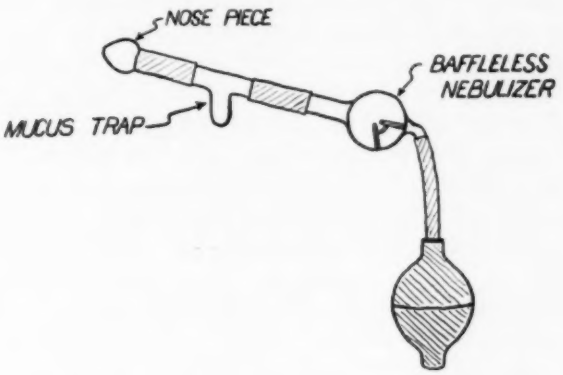

Diagram 1. Aerosol negative pressure apparatus for home use.

soluble tablet, to which has been added saline or neosynephrin, the nosepiece is attached. The patient simultaneously squeezes the rubber bulb and inhales three times. The nose is thus filled with penicillin mist. At the conclusion of the third squeeze, the opposite nostril is closed with the finger, the patient swallows as the bulb expands, thus creating a negative pressure in *all* of the nasal sinuses. Immediately, while the sensation of suction is being felt, the bulb is squeezed to re-start the cycle; this allows the aerosol to enter the sinuses as they attempt to regain atmospheric pressure. (Diagram 1.)

This nebulizer contains no baffle, and the jet is large so that the mist is made up of large particles. This accomplishes a greater deposition of penicillin in the nose, and therefore a larger concentration in the sinuses. The large particle size is also less likely to disturb patients suffering from asthma, since less of the nebulin can reach the bronchioles. The duration of the procedure is also somewhat shortened by using a larger particle mass. Penicillin has been recovered from the sinuses of patients so treated in adequate amounts, indicating that topical therapy has been accomplished.

Patients with acute and chronic sinusitis have been treated with one administration of 100,000 to 200,000 U. of penicillin per day dissolved in 1 cc. of 1 per cent neosynephrin, using 1/3 cc. for a rinse. Many patients will need more than one treatment per day, which can be easily

accomplished by the use of such a portable apparatus in the home. Acute cases may often clear without any treatment, especially those of three days' duration following a common cold. But when they persist in subacute form, often with a post-nasal drip and cough, there is frequently a striking diminution in cough and discomfort after a day or two of treatment. The acute flare-ups that sometimes follow the resolving of chronic sinusitis may be easily cleared by this method in a few days. Chronic sinusitis may require more prolonged treatment; good results have been achieved, however, in cases which have defied conventional measures for years.

While irritation of the nose is rare, plain ephedrine or neosynephrin may be used to promote drainage and ventilate the sinuses in patients allergic to penicillin. This procedure is especially applicable to children, since they may be somewhat resistant to other forms of treatment and may regard the apparatus as something of a game. There are also a few nervous adults who are refractory to repeated antral punctures.

Bronchiectasis is notoriously resistant to all conventional forms of treatment save surgery alone. Although removal of the infected tissue is indeed the only cure for bronchiectasis, aerosol therapy is valuable in inoperable cases, and also both pre-operatively and post-operatively, to reduce complications. Pathologically there is a much diminished blood flow to the walls of the dilated and diseased bronchi so that either penicillin or sulfonamide drugs administered by means other than aerosol have had little effect in controlling bronchiectasis. The absence of fever and other acute toxic symptoms of absorption is an indication that blood supply to the bronchi is diminished. In the past, postural drainage has been of great importance to the patient whose expectoration may amount to 6 ounces of sputum per day. The use of aerosol diminishes the need for postural drainage, since the majority of patients on aerosol therapy evidence a remarkable reduction of sputum in a few days. If bacteria are controlled there is not a production of sputum and therefore less need for postural drainage.

The use of a nebulizer producing particles of a correct size is of some importance. For the treatment of sinusitis large particle sizes are useful, since deposition in the nasopharynx and sinuses is particularly desirable. Measurement of the blood stream concentration is a sure way to tell how far down the nebulin has penetrated, since absorption from the alveoli themselves is at a maximum in a minimum of time. Experiments have

shown that maximum absorption occurs with a particle size of 0.8 microns; particles smaller than this exist in the air currents by Brownian movement and do not settle, and are therefore carried out of the lungs. Slightly larger particles are more satisfactory for the treatment of bronchiectasis, however; a deposition in the alveoli does surely occur, and more particles drop out on the larger passages of the lung infected as in bronchiectasis. A nebulizer that forms particles of larger size disposes of its contents in a shorter period of time, also reducing the patient's fatigue. A particle size of 1 to 3 microns in radius has been found to be optimal for aerolization of antibiotics into the lungs.

A high level of antibiotic in the sputum in bronchiectasis indicates that the pathogenic organisms are exposed to the drug. Penicillin concentrations of zero are uniformly found after even huge injections of penicillin given intramuscularly, whereas after a lesser amount of aerosol penicillin, the sputum contains measurable amounts of penicillin to levels as high as several hundreds of units per cc.

Treatment is instituted after culture of organisms present. It is important to culture sputum before instituting treatment since the presence of B. coli in the first culture indicates that it may be a pathogen for the patient. In most instances the B. coli will be seen only after a short period of treatment with penicillin. The organism may usually be eliminated easily with streptomycin, but this is generally not necessary, as apparently it is not a pathogen in these cases. Often B. coli may persist without affecting the subsequent course of the illness.

Streptomycin is of special value in the treatment of Friedländer bacillus infection in any part of the respiratory tract. Infections in the lung caused by this organism are more effectively combated by aerosol than by intramuscular injection. Although colon bacilli may be eradicated in patients with bronchiectasis, these organisms soon become resistant to streptomycin and frequently reappear after one week's treatment. Streptomycin is effective, however, in the treatment of sinusitis with primary colon bacillus infection; it may also be relied upon to eliminate other gram-negative organisms. Probably through a synergistic action, a combination of streptomycin with penicillin may be useful for a limited period of one to two weeks. Sulfonamide aerosols have been used in gram-negative infections. Patients whose condition is amenable to surgical treatment may be effectively treated with penicillin and possibly streptomycin aerosol for one week prior to treatment or until

sputum appears to be reduced to a minimum; it may be continued after surgery for a variable period of time.

For patients who have disease too far advanced to be able to undergo surgery, penicillin aerosol allows hope for a nearly normal way of life. Dosage and duration of treatment with penicillin must be adjusted to the individual case. Generally speaking, the more chronic the process, the more extensive the treatment and the longer the time required to produce a desirable effect. In some patients a greatly diminished cough and sputum will be evident in a few days, while others must be treated for a few weeks before an appreciable effect is noted. Occasionally after a few weeks of treatment a patient may remain relatively free from symptoms for months. Others will have to be treated daily to control the infection. Patients infected with an organism sensitive to penicillin have been treated daily for several years with penicillin aerosol without the development of resistant organisms. In some advanced cases in which daily treatment has been given, remarkable improvement has been maintained for years, characterized not only by a reduction in cough and sputum, but by a gain in weight and improvement in a feeling of well-being to the extent that an invalid on the verge of death has been enabled to work and carry on a life of only moderate restriction. The daily use of penicillin is not more of a chore than one to three daily injections of insulin by a diabetic. In a number of cases penicillin-resistant organisms will be demonstrated in the start of treatment, so that a less pleasant prognosis may be anticipated. However, the treatment should be tried in all cases, the dosage being increased until it is certain that the infection cannot be overcome.

The present program for the treatment of bronchiectasis consists of five daily inhalations of 100,000 U. of penicillin for hospital patients or those confined to their homes. Ambulatory patients who must work are given three inhalations per day of 200,000 U., and later two inhalations. The penicillin is dissolved in 1 cc. of saline solution or a 1 per cent neosynephrin per 100,000 U. When the solution in the nebulizer is exhausted, an additional ½ cc. of solvent is added to wash droplets of penicillin from the sides of the nebulizer to be re-nebulized. If an oxygen tank is used the flow is set for about 8 liters per minute When an automobile tire foot pump is used as the source of power, a smaller amount of solution may be used, since the physical effort exerted in nebulizing 1-2 cc. of solution is not inconsiderable.*

* A new electrical pump will soon be available at a reasonable cost.

Following inhalation of 200,000 U. of penicillin a blood concentration of 0.8 of a unit may be observed, indicating an absorption of many times the concentration needed to control penicillin-sensitive organisms in the body. Since this concentration has passed through the walls of the bronchi, it is reasonable to assume that any pathogenic organism present has been exposed to a lethal dose of the antibiotic.

Concomitant with the use of penicillin aerosol, a triple sulfonamide mixture may be administered orally to augment the effect of the aerosol.

The treatment of lung abscess by intramuscular injection of penicillin or by oral administration of sulfonamide compounds has often been followed by satisfactory recovery. Five patients who did not improve with parenteral penicillin treatment have been cured by use of aerosolized solutions of antibiotics. The use of aerosol is indicated for at least one month in cases of chronic lung abscess which have passed the stage wherein surgical drainage is of maximum benefit and in which the condition of the patient does not warrant emergency surgical intervention. Many patients may thus be saved from an operation for extirpation of the diseased area. An acute abscess of the lung should probably be given the advantage of both intramuscular and aerosol penicillin, although penicillin aerosol can penetrate into the pneumonitis surrounding the abscess and produce an effective blood level to reach a possible area behind a plugged bronchus. The addition of sulfonamides or streptomycin to the aerosol is justified in any case in which sputum culture shows gram-negative organisms. In some cases helium-oxygen may be used to carry the mist into a partially blocked portion of the lung since helium-oxygen flows through a constricted orifice with almost twice the ease enjoyed by 100 per cent oxygen. Daily inhalations of 1,000,000 U. divided into five doses, have been used in these cases.

The inhalation of powdered, micronized, or more simply, dust penicillin has recently been advocated to produce the same results as aerosol penicillin. In our experience local reactions have been found to be more numerous and more severe with dust penicillin than with aerosol. Moreover, the "dust" does not produce high blood levels, an indication that the penicillin has not penetrated deeply.

Rapidity of nebulization has been claimed as an advantage of dust penicillin. It has been our experience that a large particle size nebulizer such as that used for sinus treatment will produce its nebulin in an equally short time. Ease of administration is a factor in favor of dust

penicillin; however, the cost of dust penicillin is twice that of penicillin for nebulization, and, in long continued use, the cost of the apparatus for nebulization is more than amortized.

Systemic, local or allergic reactions may occur with penicillin aerosol. In patients with asthma, procaine penicillin is now advised to avoid the possibility of bronchospasm. In other cases, penicillin is stopped for awhile, but then should always be started again, since the reaction may not recur. A red or black tongue and a sore or red throat occasionally is seen after several days of therapy. Local reactions involving the throat may be circumvented in part by drinking water during and after the treatment.

Occasionally bronchospasm is encountered in a patient suffering from bronchiectasis. Bronchiectasis and asthma coexistent produce a therapeutic dilemma, since penicillin aerosol may produce severe reactions of bronchospasms in an asthmatic patient. To combat bronchospasm, inhalations of nebulized epinephrine are prescribed prior to inhalation of penicillin. Occasionally oral ingestion of aminophyllin may suffice.

THE CONTINUED USE OF OXYGEN FOR PREMATURE INFANTS*

CLEMENT ANDREW SMITH

Boston Lying-In Hospital, Boston

PERHAPS the most practical way to survey this subject will be to put the information in the form of questions and answers. The terms "oxygen therapy" or "putting the baby in oxygen" will be used to mean raising the oxygen content of the atmosphere the infant breathes. The most troublesome question is the first:

1. *How important a factor is continued oxygen therapy in saving the lives of premature babies?*

It is an odd fact that no exact statistical evaluation of this procedure has been found in the literature. We use a great deal of oxygen in our two

* From the Laboratory for Research on the Newborn, Boston Lying-In Hospital, the Children's Hospital, and the Department of Pediatrics, Harvard Medical School, Boston.
Read December 6, 1949 in the Pediatric Meeting of the Symposium on Inhalational Therapy at The New York Academy of Medicine.

premature infant nurseries, as everyone else does. And yet, I can find no arithmetical basis for measuring the beneficial effects of this procedure. In our own experience, we have never altered this factor without at the same time introducing other changes in our methods. Nor have we ever treated alternate patients with and without oxygen, and I rather hope we never shall. This singular inability to evaluate a therapeutic agent in wide use is not limited to oxygen administration for premature infants. I am told by professors of physiology and anesthesiology that they too cannot discover good mathematical demonstrations of the life-saving effects of oxygen in patients at any age. Yet there is so much evidence that the pulmonary, circulatory, and central nervous systems of premature infants are exceptionally vulnerable, we have all seen accidents and crises of a respiratory nature occur so often in such patients, and we are so familiar with the apparent improvement following oxygen administration, that it would be a very skeptical pediatrician who would demand a controlled group of patients to prove the value of oxygen administration for premature infants. It seems logical that if such patients are prone to unpredictable respiratory crises (and they are), one should offer them the protection of continuous oxygen rather than merely having oxygen at hand for use after the emergency declares itself.

2. *What do we know of the specific effects of oxygen in premature infants?*

We have as yet only hints at an answer to this question. We know by observation (and a few measurements) that the arterial oxygen saturation of young prematures may be considerably below the desirable 90 per cent or more, and sometimes without much clinical evidence of cyanosis. If the infant is free from massive atelectasis (or other left-to-right vascular shunts), this discrepancy of arterial blood saturation will be prevented or relieved by oxygen administration. We also know from the work of Wilson and others, substantiated by our own observations, that oxygen administration has interesting and presumably salutary effects upon the rate and volume of respiration. Briefly put, in the normal appearing, non-cyanotic premature infant, even one several weeks old, in whom the arterial oxygen saturation is desirably above 90 per cent, respiration in air is usually periodic or otherwise irregular. Increasing the oxygen of the respired air not only regularizes this characteristically irregular respiration but also increases ventilation by as much as 25 per

cent. The relationships of these unusual oxygen effects to fetal hemoglobin, anaerobic metabolism, or to other unique properties of premature extra-uterine existence, remain unexplained. Nevertheless, additional oxygen reaching the lungs and blood obviously brings about not only expected but also certain unexpected results in premature patients.

3. *To what infants should it be given, and for how long?*

Our standing orders are that every premature infant be placed in 40 to 50 per cent oxygen for at least 24 hours after admission. We have a rule for putting the infant in oxygen; we have no rule for taking him out. The best indication for removal from oxygen is that the infant's color, activity, and general respiratory appearance remain as satisfactory upon removal as they were in the oxygen-enriched atmosphere. But we prefer to err on the side of over-caution. Our infants of around 2 lb. (800-1000G.) birth weight are gradually removed to air when their weight has passed 3 lb. (1350G.) and is steadily increasing; this may be at two months or more of age. For the 2-3 lb. (900-1400G.) group, the period averages about five or six weeks; for the 3-4 lb. (1400-1800 G.) group, perhaps three weeks, and the larger infants, the most numerous group, are kept in oxygen from 24 hours to several days. The removal to air is always performed gradually, and in each case depends on that most useful guide, careful observation.

4. *How should oxygen be administered?*

Most premature infants are kept in a closed incubator, and the addition of oxygen is thus simplified. We aim at an atmosphere of about 40-50 per cent oxygen concentration, and find that this is usually achieved in the common incubators or hoods by a flow of about 4 liters per minute. Dr. Robert Denton, one of our residents, has demonstrated that oxygen flowing at 4 liters per minute through a funnel 1 inch from the mouth of an infant in an open crib produces a concentration of about 50 per cent in the oropharynx. One additional comment is that premature nurseries are places where personnel should be kept at a minimum, where equipment should not be constantly moved in and out, and where admissions occur unpredictably. For all these reasons, a constantly available supply of oxygen piped to regularly spaced wall outlets is an especial convenience for such nurseries.

5. *May continued use of oxygen do harm to premature infants?*

Here perhaps we are in greatest ignorance. The literature suggests that lesions of oxygen poisoning are less easily produced in the lungs of young than of adult animals. It also suggests that concentrations of less than 60 per cent oxygen are without harmful results in adults, even if long administered. Chapple's observation of no untoward effects in premature infants kept at 85 per cent oxygen (humidified) for three weeks is reassuring and is often quoted. Nevertheless, someone may be carried away by the assumption that "if a little is good a lot is better." The fact remains that pulmonary damage is a remote possibility which has not yet been absolutely evaluated.

Another question of perhaps less importance, though of equal interest, is whether prolonged oxygen administration may diminish the stimulus to erythrocyte and hemoglobin production Animal experimentation has given all sorts of answers All we know of the anemia so regularly developed by premature infants indicates that other factors than oxygen supply are its primary determinants. Yet until some bold investigator follows blood formation in a large group of such infants kept entirely in air for comparison with that of a group kept in increased oxygen, we can only assume that prolonged oxygen therapy does not affect hemopoiesis in these small patients.

There appear to be sound clinical reasons for the prolonged administration of extra oxygen to premature infants, even though the possibilities of potential harm have never been evaluated. Administration is made easy by the circumstances in which such patients are usually treated. The unique respiratory status of premature infants offers a field for much further study of their physiology in general and of their response to oxygen in particular.

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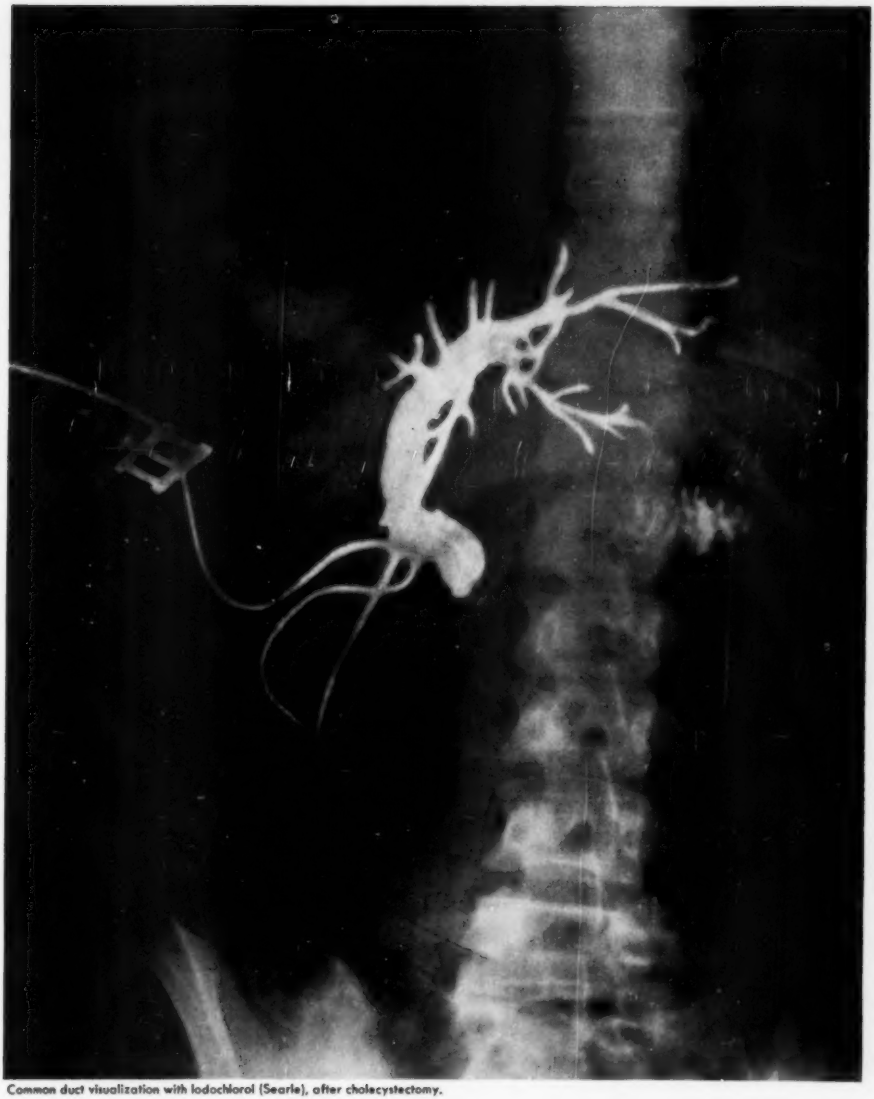

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SEARLE *RESEARCH IN THE SERVICE OF MEDICINE*

April 15, 1950

THE STATUS OF B_{12} ANTI-ANEMIA THERAPY:

Vitamin B_{12} and Folic Acid (Oral)

VITAMIN B_{12} AND FOLIC ACID, given together by mouth, have a pronounced synergistic action. A non-therapeutic amount of folic acid has been found to promote the utilization of vitamin B_{12} in oral doses formerly believed to be ineffective.

HOW DOES IT ACT?

Vitamin B_{12} for extrinsic factor-like activity

Given by mouth, vitamin B_{12} acts like the extrinsic factor of food. The effective oral dose is some 30 to 60 or more times greater than the effective parenteral dose.

Folic acid for intrinsic factor-like activity

Meyer and associates[1] assert that, in vitamin B_{12} and folic acid therapy, "folic acid acts like 'intrinsic factor'" in that it promotes utilization of vitamin B_{12}. The role of folic acid "on the release, absorption or synthesis of vitamin B_{12} in the intestinal tract" is open to speculation, according to Cartwright, Wintrobe and others.[2] Folic acid, Best and Taylor[3] state, may possibly "act to stimulate the production of the intrinsic factor or be the intrinsic factor itself."

B_{12} and folic acid are essential

Luhby and Wheeler [4] suggest:

1. If a folic acid deficiency is profound, even large doses of vitamin B_{12} are hematologically inert.
2. If a severe vitamin B_{12} deficiency exists, large doses of folic acid should be hematologically inactive.

They advance the following possible equation:

(Folic acid) x (Vitamin B_{12}) ⟶ (E.M.F.)

WHAT ARE THE RESULTS OF THERAPY?

With vitamin B_{12} and folic acid, given orally, hematologic response frequently parallels that of parenteral vitamin B_{12} therapy. Ordinarily, clinical remission is both prompt and dramatic. Furthermore, in patients so far studied, oral vitamin B_{12} and folic acid apparently protects against and reverses manifestations of combined system disease.

HOW IS IT AVAILABLE?

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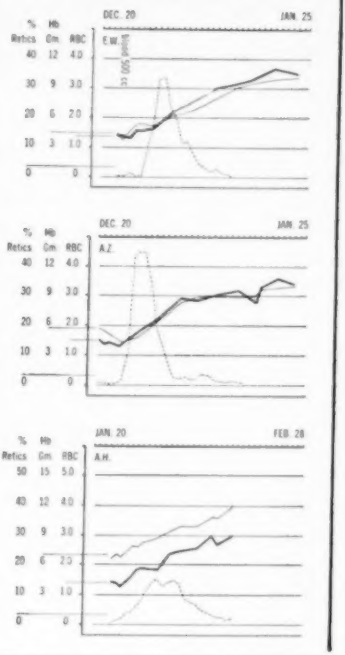
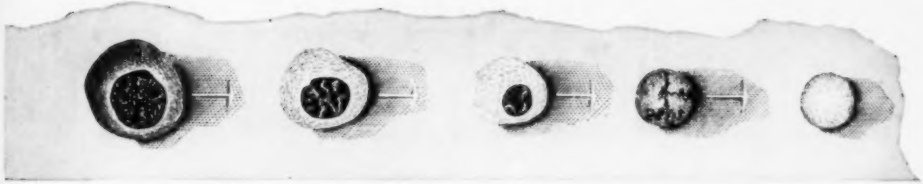
Hematologic response to 1 Rubrafolin Capsule daily



INDICATIONS FOR B_{12} THERAPY

Macrocytic anemias ordinarily respond well to vitamin B_{12} therapy. These include pernicious anemia without neurologic involvement, pernicious anemia with combined system disease, nutritional macrocytic anemia, tropical sprue, non-tropical sprue. (Pernicious anemia of pregnancy responds best to folic acid therapy.)



and Vitamin B_{12} Alone (Parenteral and Oral)

Vitamin B_{12} alone—parenteral administration

In most anemias characterized by megaloblastic arrest of the bone marrow vitamin B_{12} will:

1. Reverse megaloblastic arrest of the bone marrow.
2. Protect against and reverse neurologic changes.
3. Reverse gastrointestinal manifestations.
4. Produce rapid, marked and—in most cases—sustained clinical improvement.

Vitamin B_{12} alone—oral administration

When given alone by mouth, vitamin B_{12} is not as hematopoietically active as it is when it is injected. In the megaloblastic anemias, vitamin B_{12} is not easily absorbed by the gut. Much larger doses are necessary if a therapeutic effect is to be obtained.

	THERAPEUTIC DOSAGE	MAINTENANCE DOSAGE	REMARKS	SUPPLY
RUBRAFOLIN* (25 micrograms of vitamin B_{12}, 1.67 mg. of folic acid per Capsule).	1 Capsule daily	1 Capsule daily.	If response is submaximal at the end of 10 days or 2 weeks, double the dose. In case response is not optimal by the fourth week, the patient should be placed on parenteral Rubramin.	Bottles of 100 Capsules.
RUBRAMIN* Capsules (25 micrograms of vitamin B_{12} per Capsule).	6 to 12 Capsules daily.	To be adjusted to patient's needs.		Bottles of 100 Capsules.
RUBRAMIN 15 or 30 microgram ampuls; 5 and 10cc. vials—30 micrograms per cc.	15 to 30 micrograms once or twice a week.	15 micrograms every 2 weeks or 30 micrograms once a month.	Larger therapeutic doses must be used in the presence of moderate to severe neurologic involvement.	1 cc. ampuls, 15 or 30 micrograms of vitamin B_{12} per ampul. Boxes of 5. 5 and 10cc. vials, 30 micrograms of vitamin B_{12} per cc. also available: Solution Rubramin Crystalline (Squibb Crystalline Vitamin B_{12} Solution) in 1 cc. ampuls, containing 15 micrograms of crystalline vitamin B_{12}.

Bibliography: 1. Meyer and associates: A. J. Clin. Path. (in press). 2. Cartwright, Wintrobe and associates: Blood 4:301, 1949. 3. Best and Taylor: The Physiological Basis of Medical Practice, ed. 5, Baltimore, Williams & Wilkins, 1950, p. 87. 4. Lubby, A. L.; and Wheeler, W. E.: The Health Center Jl. (Ohio State Univ.) 3:1, 1949.

*Patients to receive Rubrafolin or Rubramin Capsules should be individually selected. The physician should rule out patients with severe gastrointestinal disturbances, severe cardiac failure or severe anemia when pernicious anemia is present. Patients such as these—and those with severe neurologic involvement—respond better to parenteral Rubramin therapy. Neurologic changes should be watched for closely. At the first sign of new neurologic involvement, the patient should be placed on parenteral Rubramin therapy.

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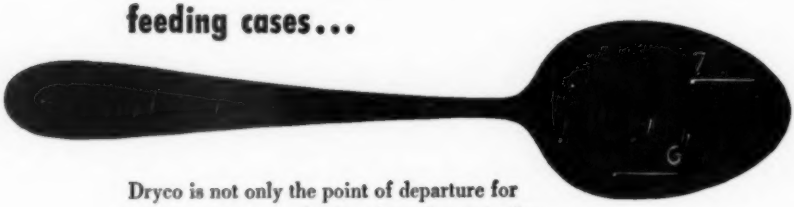

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*Pitt, C.K.: *The Art and Science of Artificial Infant Feeding*, J.M. Asso. Ala. 19:101 (Oct.) 1949.

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Smadel, J. E.: J.A.M.A. *142*:315, 1950 (discussion)

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Hewitt, W. L., and Williams, B., Jr.: New England J. Med. *242*:119, 1950

"**NO toxic reactions** or signs of intolerance were observed."

Payne, E. H.; Knaudt, J. A., and Palacios, S.: J. Trop. Med. & Hyg. *51*:68, 1948

"**NO symptoms or signs of toxic effects** attributable to the drug were observed."

Ley, H. L., Jr.; Smadel, J. E., and Crocker, T.: Proc. Soc. Exper. Biol. & Med. *68*:9, 1948

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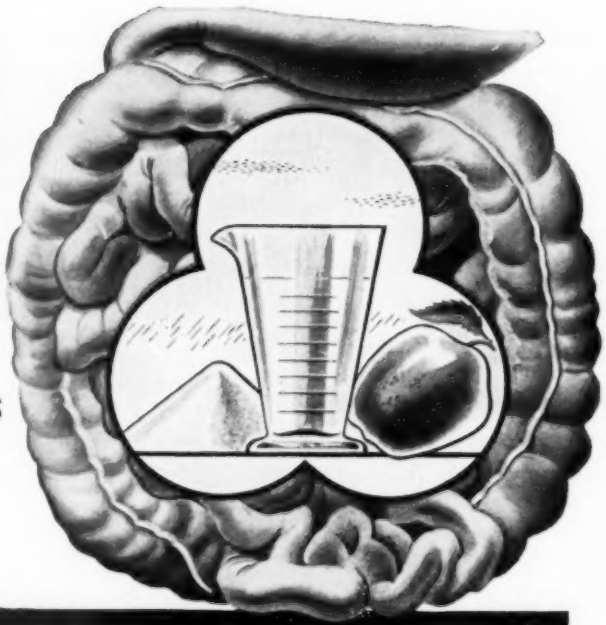

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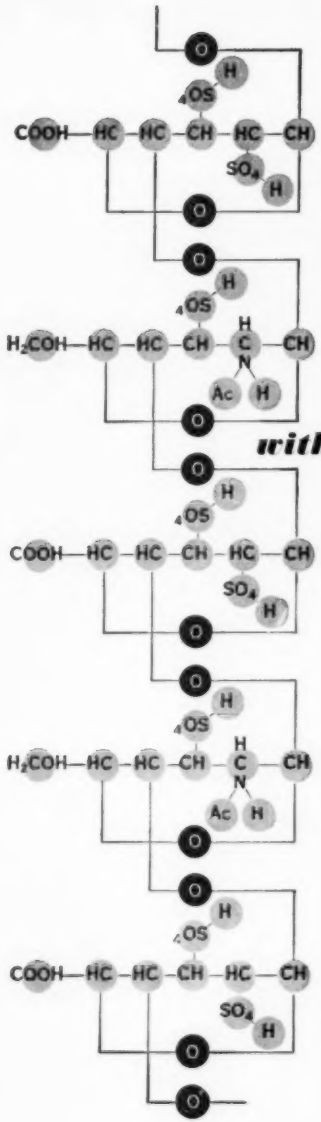

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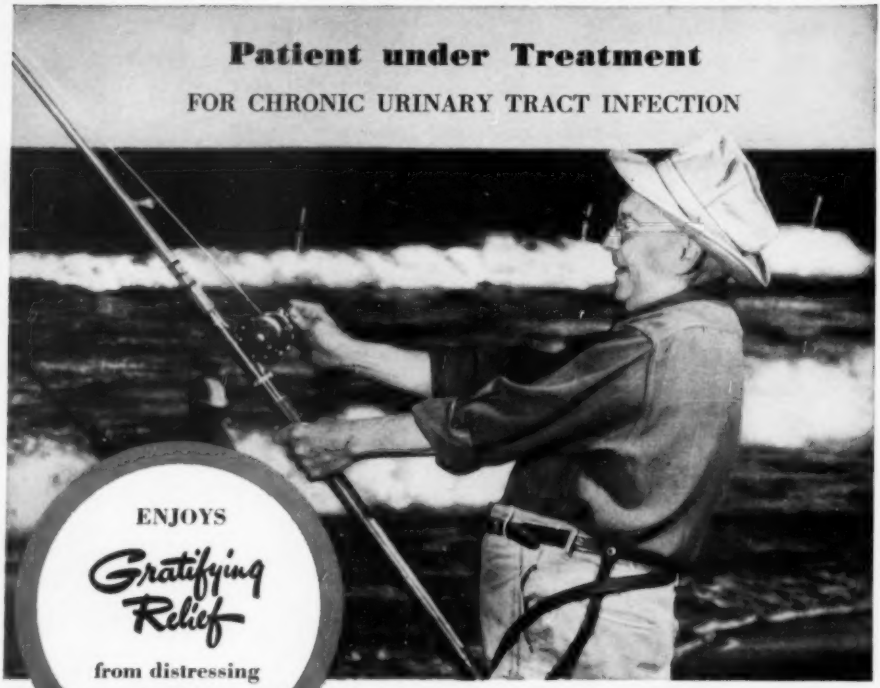

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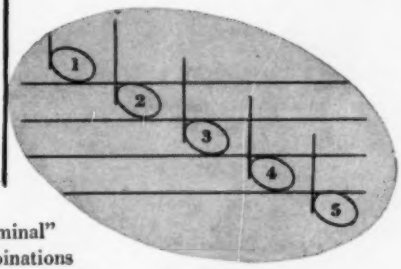

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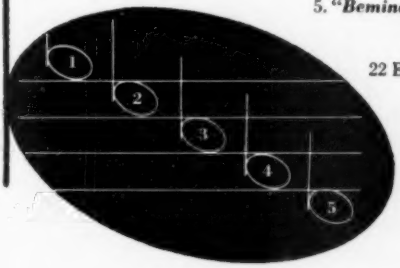

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"The geographical distribution of amebiasis is world-wide."[1] "Although amebiasis is often considered a tropical disease, it is prevalent even in certain arctic regions."[2]

INCIDENCE OF AMEBIASIS IN THE UNITED STATES

STATE	NO. EXAMINED	NO. POSITIVE	% POSITIVE
New York[3]	350	34	9.7
Pennsylvania[4]	1060	43	4.1
Minnesota[5]	5000	535	10.7
Illinois[6]	4478	601	13.4
Oklahoma[7]	924	92	10.0
Washington[8]	1526	164	10.7
California[9]	1341	92	6.9
Louisiana[10]	4270	355	8.3
Tennessee[11]	20,237	2,305	11.4
New Mexico[12]	1284	190	14.8
Total	**40,470**	**4,411**	**10.9**

Intestinal. Comparative in vitro studies have shown that Milibis, the new intestinal amebacide, is the most powerful of the drugs commonly used against Endamoeba histolytica. In clinical tests Milibis has given excellent results in thousands of cases. In 82.6 per cent of those that could be followed parasitologically for prolonged periods, negative stools were obtained consistently after one to four courses of Milibis treatment.[13] There were virtually no side effects.

Dose for adults: 0.5 Gm. three times daily for seven days. If stools remain positive, course should be repeated. Supplied in tablets of 0.25 Gm., bottles of 50, and 0.5 Gm., bottles of 25.

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1. Craig, C. F.; 2. Almy, T. P.; 3. Towse, R. C., et al.; 4. Wenrich, D. H., et al.; 5. Sanford, M. F.; 6. Spector, B. K.; 7. McMullen, D. B., and Gray, J. K.; 8. Cresswell, S. M., and Wallace, C. E.; 9. Wight, T.; 10. Faust, E. C., and Headlee, W. H.; 11. Meleney, H. E., et al; 12. Spector, B. K., and Hardy, A. V.; 13. Berberian, D. A.; 14. Conan, N. J.; 15. Shookhoff, H. B.; 16. Sodeman, W. A.; 17. Murgatroyd, F., and Kent, R. P.; 18. Bosnuevo, J., and Estorli, E. G.; 19. D'Antoni, J. S.; 20. Manson-Bahr, P.; 21. Emmett, J. Full bibliography on request.

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ENCOURAGING results with Banthine in a group of refractory peptic ulcer patients were reported by Longino, Grimson, Chittum and Metcalf[1] and later in an enlarged series of patients by Grimson and Lyons[2]. Their observations interested other investigators[3-5] who have obtained equally promising results with this new drug.

These early observers[1,2] noticed that symptoms are sometimes relieved as soon as fifteen minutes following the institution of therapy, and in patients with long-standing, intractable pain discomfort becomes mild and intermittent or disappears. Their conclusions regarding healing of the ulcer are based on roentgenographic evidence.

Thorough pharmacologic investigations indicate that Banthine is a potent but safe drug in therapeutic doses. In these studies no abnormality of the blood or urine or other evidence of toxicity was observed.

BANTHINE: THE DRUG

Chemically, Banthine is β-diethylaminoethyl xanthene-9-carboxylate methobromide. Its generic name is methantheline bromide. It should be noted that the xanthene group bears no relation to the more familiar xanthine group of drugs.

A True Anticholinergic

Banthine may be described as a true anticholinergic drug. In therapeutic doses it controls autonomic stimuli which result in the vagotonia characteristic of the ulcer diathesis. This action is effected at

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the ganglions of both the sympathetic and parasympathetic systems and, in addition, at the postganglionic nerve endings of the parasympathetic system alone. Thus, the resulting therapeutic action is that of control of excessive parasympathetic stimuli effecting a consistent reduction of gastric hypermotility and, in most patients, a reduction in the hyperacidity which is commonly associated with peptic ulcer.

ADMINISTRATION

Because of the prominence of emotional or situational stresses in the ulcer patient and because these stresses vary in each patient, it is necessary to adjust Banthine dosage to meet individual requirements. Initial dosage may be 50 or 100 mg. (one or two tablets) every six hours, day and night, with subsequent adjustment to the patient's needs and tolerance. In addition, the usual adjunctive measures of diet, rest and relaxation should be prescribed for at least the first few weeks of treatment.

It is important that the usual high night secretions be controlled. To this end it is recommended that the night dose be taken six hours prior to the usual time of arising. Further, after the ulcer is healed, it is important that the patient be placed on a maintenance dosage schedule if he is to have a reasonable assurance of nonrecurrence. The maintenance dosage may well be approximately one-half the therapeutic dose and no evidence of chronic toxicity has been observed in maintenance dosage although this experience covers only a period of sixteen months.

Patients may report dryness of the mouth, mild degrees of blurring of vision, slight difficulty of urination or gastric fulness; these symptoms usually decrease or disappear on continued medication but if they are severe they may require dosage adjustment. Untoward reactions with Banthine therapy have not been encountered.

More complete suggestions for Banthine administration are available to the medical profession in Searle Reference Manual No. 40.

Banthine is a product of Searle research. G. D. Searle & Co., Chicago 80, Illinois.

REFERENCES

1. Longino, F. H.; Grimson, K. S.; Chittum, J. R., and Metcalf, B. H.: An Orally Effective Quaternary Amine, Banthine, Capable of Reducing Gastric Motility and Secretions, Gastroenterology 14:301 (Feb.) 1950.
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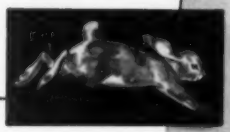

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1. Behrman, H. T., Combes, F. C., Bobroff, A., and Leviticus, R.: Industrial Med. & Surg. 18:512, 1949.

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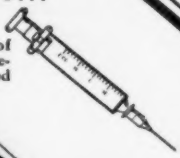

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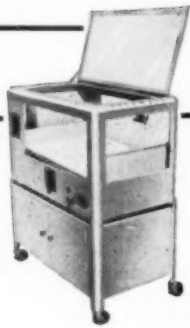

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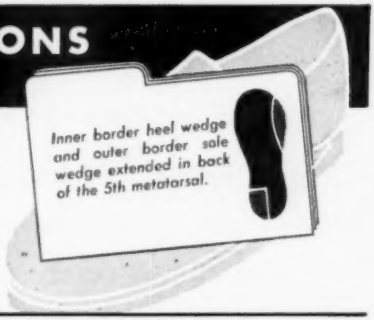

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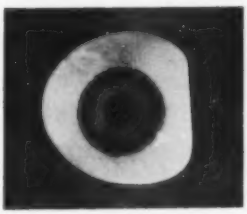

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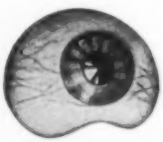

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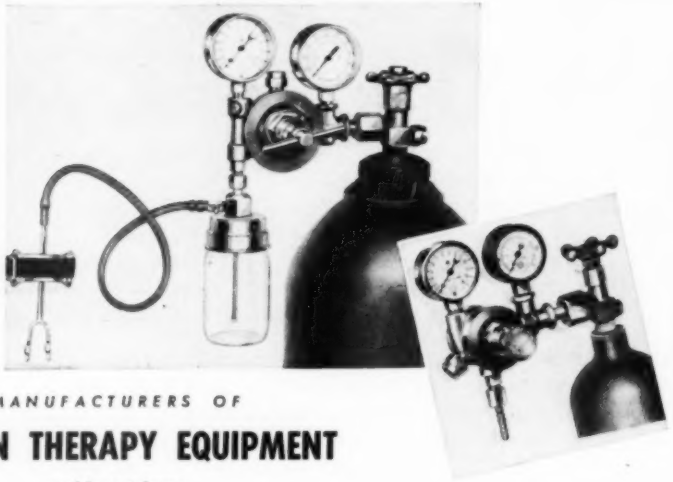

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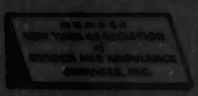

Assurance of Good Oxygen Therapy and a High Standard of Ethics

The seal of the New York Association of Oxygen and Ambulance Services, Inc. stands for competence, dependability and integrity in the field of inhalation therapy, private ambulance service, and the rental of sick-room equipment. The various companies privileged to display it do by far the biggest volume of these businesses in the Metropolitan Area.

They are bound by agreement and with a surety company bond to adhere faithfully to a high standard of ethics designed to preserve the essential qualities of fair competition, and for the protection and well-being of patients.

Rigidly enforced is a firm policy against the payment of any fees or commissions which public inquiry and Association surveys indicate have sometimes influenced the choice or recommendation of similar services.

The Symposium on Inhalation Therapy at which papers reprinted in this journal were read was held by the New York Academy of Medicine, December 5th to 10th, 1949 in cooperation with this Association.

N. Y. Assn. of Oxygen & Ambulance Services, Inc.

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